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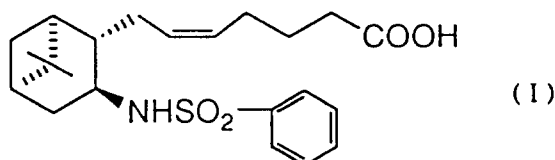
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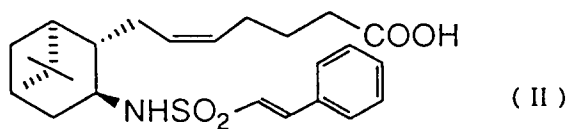
54 **Carbocyclic sulfonamides as agonists or antagonists of PGEZ.**

57 (1) Prostaglandin (PG) E₂ antagonist or agonist containing carbocyclic sulfonamides represented by the compound of the formula (I):



cyclodextrin clathrates thereof, non-toxic salts thereof as active ingredient,
(2) carbocyclic sulfonamides represented by the compound of the formula (II):

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cyclodextrin clathrates thereof, non-toxic salts thereof,

(3) process for the preparation of the compound represented by the compound of the formula (II) described hereinbefore,

(4) PGE₂ antagonist or agonist containing the compound represented by the compound of the formula (II) as active ingredient.

The compounds represented by the compounds of the formula (I) and (II) can be adapted to medicines which possess an inhibitory effect of uterine contraction, an analgetic action, an inhibitory effect of digestive peristalsis, a sleep-inducing effect as PGE₂ antagonists, and an uterine contractile activity, a promoting effect of digestive peristalsis, a suppressive effect of gastric acid secretion, a hypotensive activity as PGE₂ agonists, because they bind onto PGE₂ receptor and have an activity of antagonist or agonist against the action thereof.

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Background

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That is, the specification of the United States Patent No. 5168101 discloses sulfonamide compounds of the formula:



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wherein $\text{R}^{1\text{a}}$ is

- 10 i) $\text{COOR}^{11\text{a}}$,
 ii) $\text{CH}_2\text{OR}^{12\text{a}}$ or
 iii) $\text{CONR}^{13\text{a}}\text{R}^{14\text{a}}$

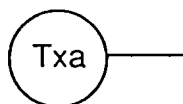
in which $\text{R}^{11\text{a}}$ is hydrogen, C1-20 alkyl, carbocyclic ring unsubstituted or substituted by C1-4 alkyl, alkoxy or halogen, or steroid;

$\text{R}^{12\text{a}}$ is hydrogen or $\text{COR}^{15\text{a}}$;

- 15 $\text{R}^{13\text{a}}$ and $\text{R}^{14\text{a}}$ each, independently, is hydrogen, C1-4 alkyl or $\text{NR}^{13\text{a}}\text{R}^{14\text{a}}$ is amino acid residue or heterocyclic ring;

$\text{R}^{15\text{a}}$ is C1-4 alkyl or phenyl;

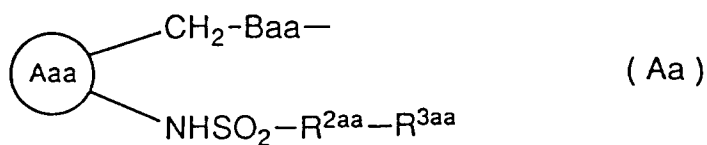
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25 is

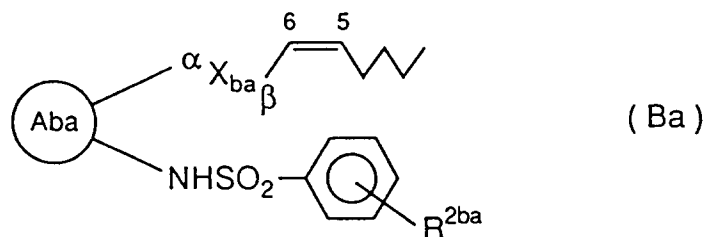
i)

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ii)

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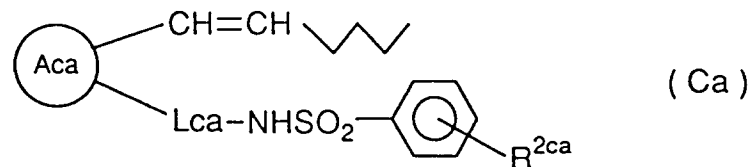


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or

iii)

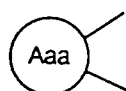
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50

in which

55



5

is

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i)



(Aaa - 1) ,

ii)



(Aaa - 2) ,

15

iii)



(Aaa - 3) ,

20

iv)



(Aaa - 4) ,

25

v)



(Aaa - 5) ,

30

vi)



(Aaa - 6) ,

vii)



(Aaa - 7) ,

35

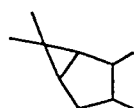
viii)



(Aaa - 8) ,

40

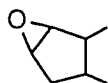
ix)



(Aaa - 9) ,

45

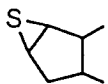
x)



(Aaa - 10) or

50

xi)



(Aaa - 11) ;

55

Baa is

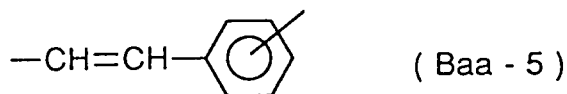
i) $-\text{CH}_2-\text{CH}_2(\text{CH}_2)_{\text{ma}}-$ (Baa-1),

ii) $\text{cis-CH}=\text{CH}(\text{CH}_2)_{\text{ma}}-$ (Baa-2),

iii) $-\text{CH}_2-\text{O}(\text{CH}_2)_{\text{ma}}-$ (Baa-3),

iv) $-\text{S}(\text{CH}_2)_{\text{ma}}-$ (Baa-4) or

v)

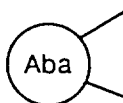


in which ma is 1-6, a double bond is E, Z and EZ mixture and phenylene is o-, m- or p-phenylene in the formula (Baa-5) ;

$\text{R}^{2\text{aa}}$ is a single bond or C1-4 alkylene;

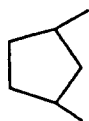
$\text{R}^{3\text{aa}}$ is carbocyclic ring or heterocyclic ring unsubstituted or substituted by one to three of C1-4 alkyl, C1-4 alkoxy, hydroxy, carboxyl, cyano, halogen or nitro or

$\text{R}^{2\text{aa}}$ and $\text{R}^{3\text{aa}}$ taken together, is C1-12 alkyl;



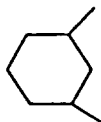
is

i)



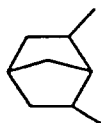
(Aba - 1) ,

ii)



(Aba - 2) ,

iii)



(Aba - 3)

or

iv)



(Aba - 4)

;

Xba is

i) a single bond,

ii) C1-4 alkylene or

iii) C2-4 alkenylene,

with the proviso that, $\alpha\text{CH}=\text{CHCH}_2\beta$ and $\alpha\text{CH}_2\text{CH}=\text{CHCH}_2\beta$ are excluded;

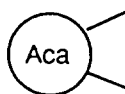
R^{2ba} is

i) hydrogen,

ii) halogen or

iii) C1-4 alkyl;

the configuration of a double bond between C5-C6 in the formula (Ba) is cis;



is

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i)



(Aca - 1) ,

10

ii)



(Aca - 2) ,

15

iii)



(Aca - 3) ,

20

iv)



(Aca - 4) ,

25

v)



(Aca - 5) ,

30

vi)



(Aca - 6) ,

35

vii)



(Aca - 7)

or

viii)



(Aca - 8) ;

40

Lca is C1-4 alkylene;

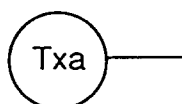
R^{2ca} is hydrogen, C1-4 alkyl or halogen;

the configuration of a double bond between C5-C6 in the formula (Ca) is cis or trans;

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with the proviso that, when

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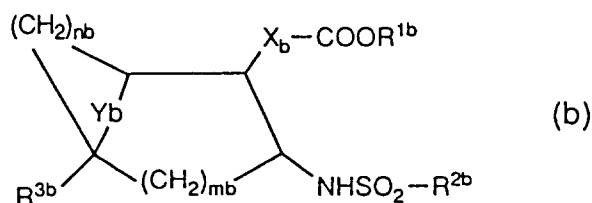


is the formula (Aa), R^{11a} is not hydrogen and C1-20 alkyl ;

cyclodextrin clathrates thereof and non-toxic acid salts thereof, when R^{11a} is hydrogen or NR^{13a}R^{14a} is amino acid residue.

55

The specification of the United States Patent No. 4861913 discloses bicyclosulfonamide derivatives of the formula:



10 wherein R^{1b} is hydrogen or lower alkyl (C1-8);

R^{2b} is alkyl, aryl or substituted aryl, aralkyl or heterocyclic ring;

R^{3b} is hydrogen or methyl;

X_b is alkylene or alkenylene which may be substituted fluorine or contained oxygen, sulfur and/or phenylene in the chain;

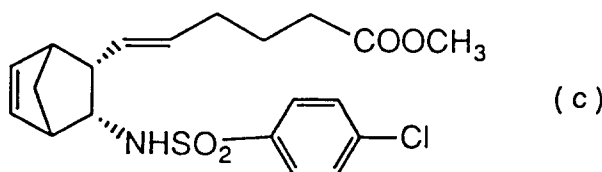
Y_b is straight or branched alkylene or alkenylene, oxygen or sulfur;

m_b is 0 or 1;

n_b is 0, 1 or 2;

and salts thereof.

20 Further, Bayer AG published the following compound in International Symposium on the chemistry of Natural Products at from May, 29 to June, 3, 1988.



Comparison with the Related Arts

35 As mentioned above, the compounds of the formula (I_x), except for a part thereof, are overlapped with those of the formulae (a), (b) and (c) described in related arts.

However, the compounds of the formula (a), (b) and (c) are disclosed only to be useful for TXA₂ antagonist. The disclosure does not suggest the use as PGE₂ antagonists or agonists which is made clear in the present invention.

40 TXA₂ has been known to have activities of platelet aggregation, aorta contraction, thrombi formation, etc., and therefore, TXA₂ antagonist is considered to be useful for antiinflammatory agents, antithrombotic agents, treatment of cardiac infraction.

Meanwhile, as mentioned above PGE₂ has been known to have an uterine contractile activity, a pain-inducing effect, a promoting effect of digestive peristalsis, an awaking effect, a suppressive effect of gastric acid secretion, a hypotensive activity etc. Therefore, PGE₂ antagonists are considered to inhibit an uterine contraction, to have an analgetic action, to inhibit a digestive peristalsis, to induce a sleep, and PGE₂ agonists are considered to contractile an uterine, to promote a digestive peristalsis, to suppress a gastric acid secretion, to low a blood pressure.

As understood from the above fact, PGE₂ antagonist or agonist differs from TXA₂ antagonist in active site, mechanism, application and property thereof. So it is difficult to expect that compounds have both actions at the same time.

The compounds of the formula (I_y) of the present invention differ from those of the formulae (a), (b) and (c) in the structure and the pharmacological action thereof. So the compound of the formula (I_y) can not be expected easily from these compounds.

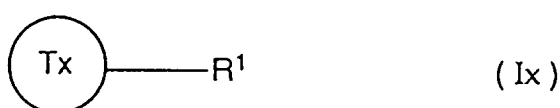
55 That is, in the structural view point, all the compounds of the formula (I_y) have a double bond between a sulfonamide group (NR⁴⁰⁰-SO₂) and the end of ω-chain (R⁵⁰⁰). The compounds differ from the compounds of the formulae (a), (b) and (c) in this point.

In the pharmacological view point, PGE₂ antagonism or PGE₂ agonism has nothing to do with TXA₂ antagonism. Therefore, PGE₂ antagonism or PGE₂ agonism of the compound of the formula (Iy) can not be expected from TXA₂ antagonism of the compound of the formulae (a), (b) and (c). There is no suggestion in any of the related arts mentioned above that PGE₂ antagonism or PGE₂ agonism is maintained even though a double bond introduces in ω -chain.

Disclosure of the Invention

The present invention is related to a novel use of known compounds, novel compounds, process for the preparation of the novel compounds and a use of the novel compounds.

Accordingly, the present invention is related to
(1) prostaglandin E₂ antagonists or PGE₂ agonists which comprises carbocyclic sulfonamides of the formula:



wherein R¹ is

i) COOR¹¹ or

ii) CONR¹³R¹⁴

in which R¹¹ is hydrogen, C1-20 alkyl;

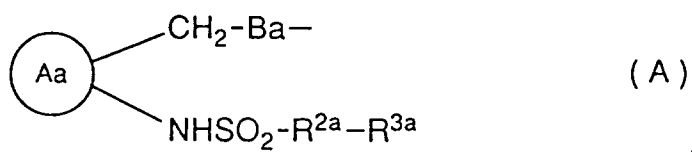
R¹³ and R¹⁴ each, independently, is hydrogen, C1-4 alkyl or

NR¹³R¹⁴ is amino acid residue;

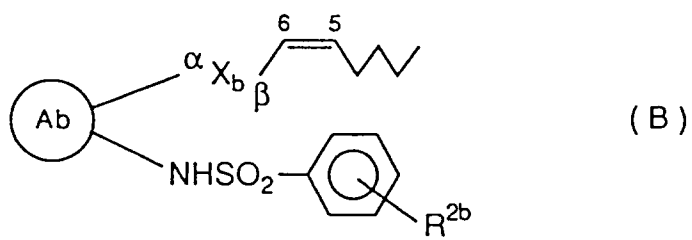


is

i)

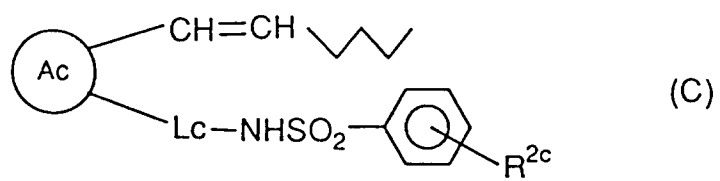


ii)

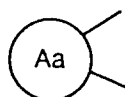


or

iii)



in which



is

i)



(Aa - 1) ,

ii)



(Aa - 2) ,

iii)



(Aa - 3) ,

iv)



(Aa - 4) ,

v)



(Aa - 5) ,

vi)



(Aa - 6)

or

vii)



(Aa - 7) ;

Ba is

i) $-\text{CH}_2-\text{CH}_2(\text{CH}_2)_m-$ (Ba-1) or

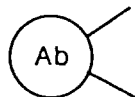
ii) $\text{cis-CH}=\text{CH}(\text{CH}_2)_m-$ (Ba-2)

in which m is 1-6;

R^{2a} is a single bond or C1-4 alkylene;

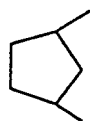
R^{3a} is benzene, naphthalene or C4-7 cycloalkyl unsubstituted or substituted by one to three of C1-4 alkyl, C1-4 alkoxy, hydroxy, cyano, halogen, trifluoromethyl or nitro or

R^{2a} and R^{3a} taken together, is C1-12 alkyl;



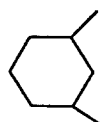
is

i)



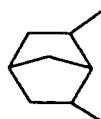
(Ab - 1) ,

ii)



(Ab - 2) ,

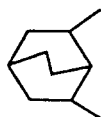
iii)



(Ab - 3)

or

iv)



(Ab - 4)

;

Xb is

i) a single bond,

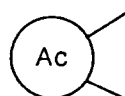
ii) C1-4 alkylene or

iii) C2-4 alkenylene,

with the proviso that, $\alpha\text{CH}=\text{CHCH}_2^\beta$ and $\alpha\text{CH}_2\text{CH}=\text{CHCH}_2^\beta$ are excluded;

R^{2b} is hydrogen, C1-4 alkyl, C1-4 alkoxy, hydroxy, cyano, halogen, trifluoromethyl or nitro;

the configuration of a double bond between C5-C6 in the formula (B) is cis;



is

i)



(Ac - 1) ,

ii)

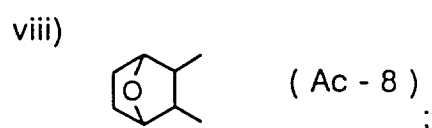
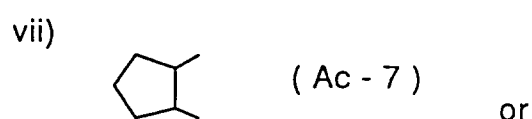
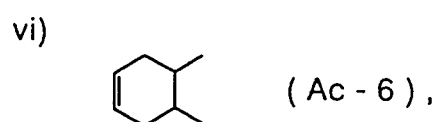
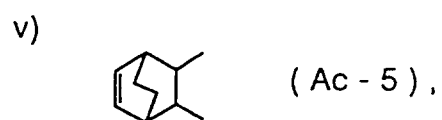
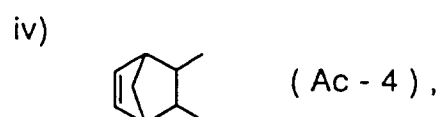


(Ac - 2) ,

iii)



(Ac - 3) ,



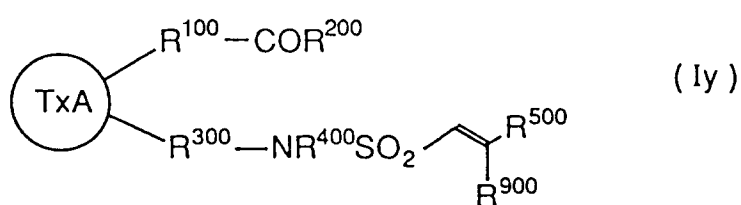
Lc is C1-4 alkylene;

R^{2C} is hydrogen, C1-4 alkyl, C1-4 alkoxy, hydroxy, cyano, halogen, trifluoromethyl or nitro;

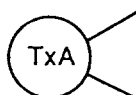
the configuration of a double bond between C5-C6 in the formula (c) is cis or trans ;

cyclodextrin clathrates thereof or non-toxic acid salts thereof, when R¹¹ is hydrogen or NR¹³R¹⁴ is amino acid residue, as active ingredient,

(2)-1 carbocyclic sulfonamides of the formula:

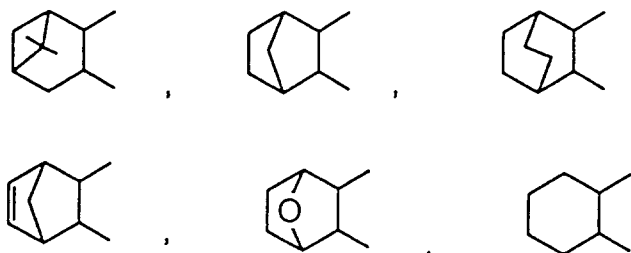


wherein



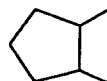
is

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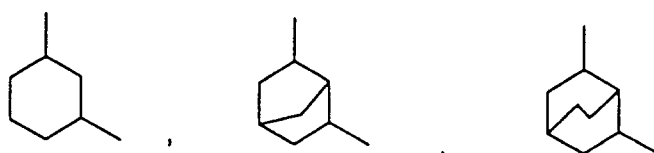
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or



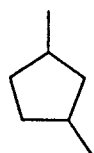
or

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or

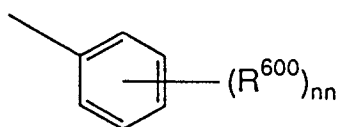


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i)

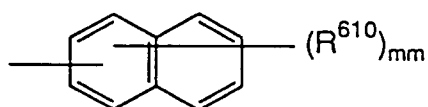
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ii)

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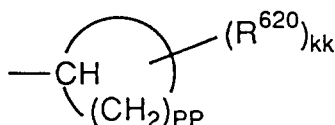


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15

mm is 1, 2 or 3;
iii)

5



10 in which R⁵²⁰ is hydrogen, C1-4 alkyl, C1-4 alkoxy, hydroxy, halogen, trifluoromethyl, nitro;
kk is 1, 2 or 3;
pp is 3, 4, 5, or 6;
iv) C1-7 alkyl or
v) hydrogen ;

15 cyclodextrin clathrates thereof or non-toxic salts thereof,
(2)-2 process for the preparation of the compounds of the formula (Iy) and
(2)-3 prostaglandin E₂ antagonists or agonists which comprises the compounds of the formula (Iy) as
active ingredient.

The terms of alkyl, alkylene, alkenylene and alkoxy in description of each symbol throughout the present specification including claims mean straight-chain or branched-chain alkyl, alkylene, alkenylene and alkoxy. The configuration of double bonds in alkenylene are E, Z and E, Z mixtures.

The presence of asymmetric centers leads, as is well known, to the existence of isomers. And all each optical isomers and all mixtures thereof are included in the formula (Ix) and (Iy). For instance, a mixture of one optical isomer and enantiomer thereof, a racemate which is an equivalent mixture especially and a mixture of one optical isomer and diastereomer thereof are also included.

In the structural formula throughout the present specification dotted line

30



indicate α -configuration, tapered line

35



indicate β -configuration.

In the formula (Ix) and (Iy), for example, the ring structures of the formula:

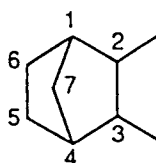
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is named each and numbered at each position as follows.

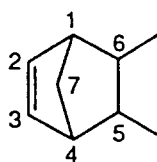
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(Aa - 1)

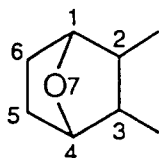
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bicyclo[2.2.1]heptane,



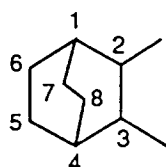
(Aa - 2)

bicyclo[2.2.1]hept-2-ene,



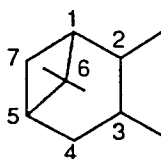
(Aa - 3)

7-oxa-bicyclo[2.2.1]heptane,



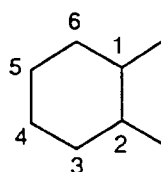
(Aa - 4)

bicyclo[2.2.2]octane,



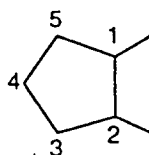
(Aa - 5)

6,6-dimethylbicyclo[3.3.1]heptane,



(Aa - 6)

cyclohexane,



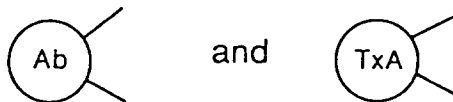
(Aa - 7)

cyclopentane

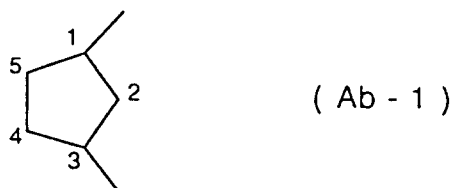
As will be apparent to those skilled in the art, the ring structures described above have two [in case of the formula (Aa-4), (Aa-6) and (Aa-7)] or four [in case of the formula (Aa-1), (Aa-2), (Aa-3) and (Aa-5)] asymmetric carbons. Namely, they are 1-, 2-, 3- and 4- position carbons in the formula (Aa-1) and (Aa-3), 1-

, 4-, 5- and 6-position carbons in the formula (Aa-2), 2-and 3- position carbons in the formulae (Aa-4), 1- and 2- position carbons in the formula (Aa-6) and (Aa-7) and 1-, 2-, 3- and 5- position carbons in the formula (Aa-5).

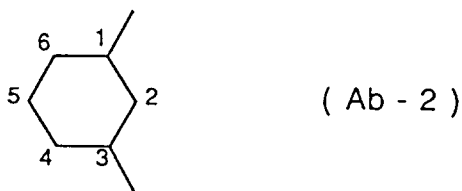
And, in the formula (Ix) and (Iy), the ring structures of the formula:



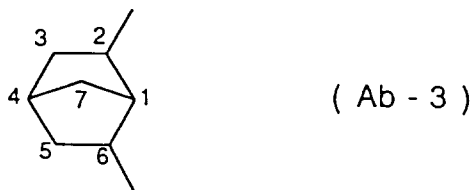
is named each and numbered at each position as follows.



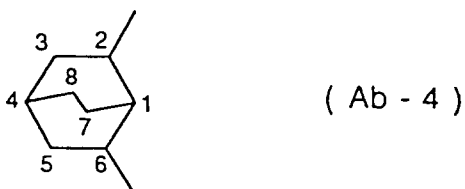
cyclopentane,



cyclohexane,



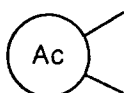
bicyclo[2.2.1]heptane,



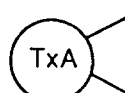
bicyclo[2.2.2]octane

As will be apparent to those skilled in the art, the ring structures described above have asymmetric carbons. Namely, the ring structures of the formula (Ab-1) and (Ab-2) have two asymmetric carbons (1- and 3-position carbons), and the ring structures of the formula (Ab-3) and (Ab-4) have four asymmetric carbons (1-, 2-, 4- and 6- position carbons).

And, in the formula (Ix), the ring structures of the formula:



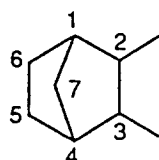
and



5

is named each and numbered at each position as follows.

10

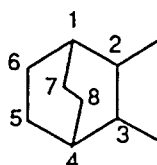


(Ac - 1)

15

bicyclo[2.2.1]heptane,

20

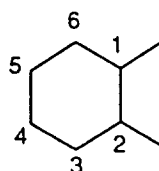


(Ac - 2)

25

bicyclo[2.2.2]octane,

30

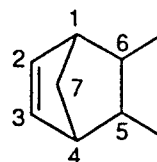


(Ac - 3)

35

cyclohexane,

40

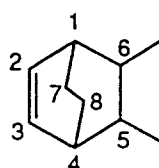


(Ac - 4)

45

bicyclo[2.2.1]hept-2-ene,

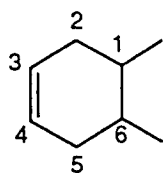
50



(Ac - 5)

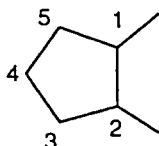
55

bicyclo[2.2.2]oct-2-ene,



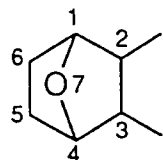
(Ac - 6)

cyclohex-3-ene,



(Ac - 7)

cyclopentane,



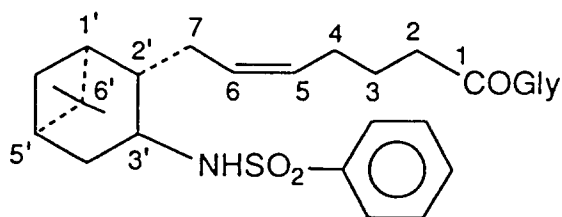
(Ac - 8)

7-oxa-bicyclo[2.2.1]heptane

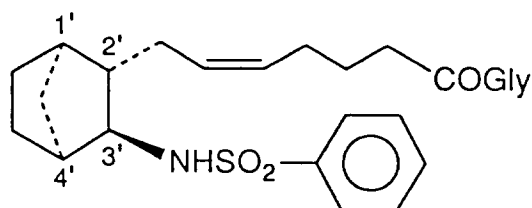
As will be apparent to those skilled in the art, the ring structures described above have two [in case of the formula (Ac-2), (Ac-3), (Ac-6) and (Ac-7)] or four [in case of the formula (Ac-1), (Ac-4), (Ac-5) and (Ac-8)] asymmetric carbons. Namely, they are 2- and 3-position carbons in the formula (Ac-2), 1- and 2-position carbons in the formula (Ac-3) and (Ac-7), 1- and 6-position carbons in the formula (Ac-6), 1-, 2-, 3- and 4-position carbons in the formula (Ac-1) and (Ac-8), 1-, 4-, 5- and 6-position carbons in the formula (Ac-4) and (Ac-5).

The steric structures of each isomers or racemates are shown by absolute configuration, for example, as follows.

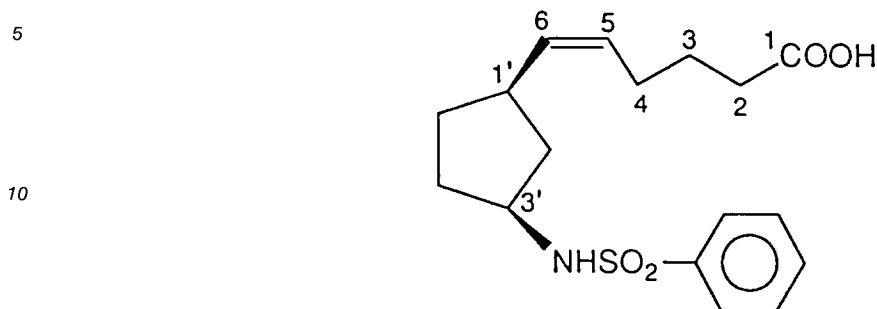
(i) in case of an optically active substance



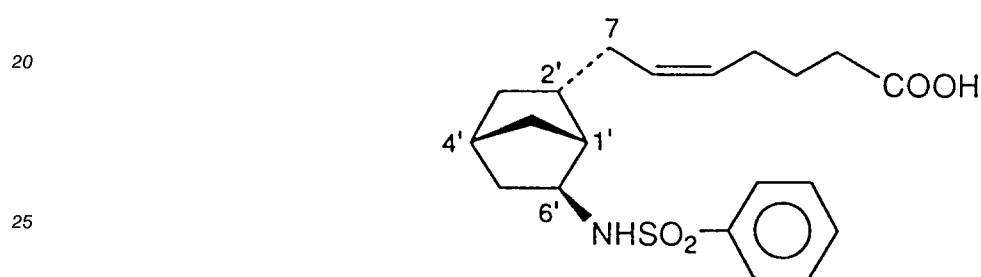
amide of (5Z)-7-[(1S,2S,3S,5R)-3-phenylsulfonylamino-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]hept-5-enoic acid and glycine



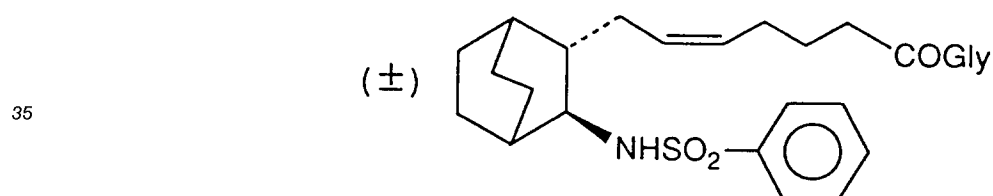
amide of (5Z)-7-[(1R,2S,3S,4S)-3-phenylsulfonylaminobicyclo[2.2.1]heptan-2-yl]hept-5-enoic acid and glycine



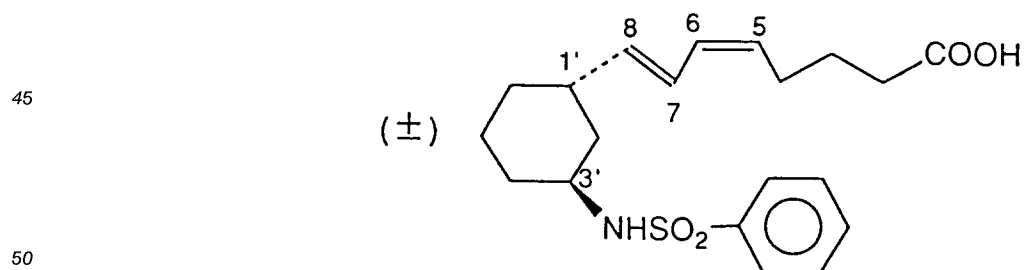
(5Z)-6-[(1R,3S)-3-phenylsulfonylaminocyclopentyl]hex-5-enoic acid



(5Z)-7-[(1R,2R,4R,6S)-6-phenylsulfonylaminobicyclo[2.2.1]heptan-2-yl]hept-5-enoic acid
(ii) in case of racemate



40 amide of (5Z)-7-[(2S*,3S*)-3-phenylsulfonylaminobicyclo[2.2.2]octan-2-yl]hept-5-enoic acid and glycine



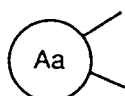
(5Z,7E)-8-[(1S*,3S*)-3-phenylsulfonylaminocyclohexyl]oct-5,7-dienoic acid

In the formula (Ix), C1-20 alkyl represented by R¹¹ means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl and isomeric groups thereof. Preferable R¹¹ are methyl, ethyl, propyl, isopropyl, 1-ethylpropyl, hexyl, octyl, decyl, dodecyl. It's also preferable that R¹¹ is hydrogen.

In the formula (Ix), C1-4 alkyl represented by R^{13} and R^{14} means methyl, ethyl, propyl, butyl and isomeric groups thereof.

In the formula (Ix), amino acid residues represented by $NR^{13}R^{14}$ mean α -amino acid residues wherein a hydrogen in the amino is removed. For example, they are glycine, alanine, valine, isoleucine, leucine, serine, threonine, proline, asparagine, glutamine, methionine, phenylalanine, tyrosine, aspartic acid, glutamic acid or lysine residue. Preferable amino acid residue are glycine, alanine, glutamic acid, lysine residue.

Preferable the ring structure of the formula:



is bridged rings represented by the formula (Aa-1), (Aa-4), (Aa-5), (Aa-6) and (Aa-7).

In the formula (Ix), out of groups represented by Ba, the formula (Ba-2) having a double bond is preferred.

In the formula (Ix), the formula $-(CH_2)_m-$ means methylene, ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene, and preferable group is trimethylene.

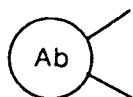
In the formula (Ix), R^{2a} means a single bond or C1-4 alkyl. C1-4 alkyl means methyl, ethyl, propyl, butyl and isomeric groups thereof. Preferable R^{2a} is a single bond.

In the formula (Ix), C4-7 cycloalkyl represented by R^{3a} means cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

In the formula (Ix), C1-4 alkyl represented by substituents in R^{3a} means methyl, ethyl, propyl, butyl and isomeric groups thereof, C1-4 alkoxy means methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof, and halogen means fluorine, chlorine, iodine and bromine.

In the formula (Ix), C1-12 alkyl represented by R^{2a} and R^{3a} taken together means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and isomeric groups thereof, and all groups are preferable.

All the rings represented by the formula:



are preferable.

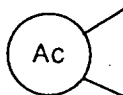
In the formula (Ix), C1-4 alkylene represented by Xb means methylene, ethylene, trimethylene, tetramethylene and isomeric groups thereof.

In the formula (Ix), C2-4 alkenylene represented by Xb means vinylene, propenylene, butenylene, butadienylene and isomeric groups thereof.

Preferable Xb is a single bond, methylene, ethylene and vinylene. Especially preferable group is a single bond.

In the formula (Ix), C1-4 alkyl represented by R^{2b} means methyl, ethyl, propyl, butyl and isomeric groups thereof, C1-4 alkoxy represented by R^{2b} means methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof, and halogen means fluorine, chlorine, iodine and bromine and all groups are preferable. It's also preferable that R^{2b} is hydrogen.

Preferable the ring structure of the formula:



is the groups represented by the formula (Ac-1), (Ac-3), (Ac-4) and (Ac-7).

In the formula (I_x), C1-4 alkylene represented by L_c means methylene, ethylene, trimethylene and tetramethylene, and preferable groups are methylene and ethylene.

In the formula (I_x), C1-4 alkyl represented by R^{2c} means methyl, ethyl, propyl, butyl and isometric groups thereof, and preferable groups is methyl. C1-4 alkoxy represented by R^{2c} means methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof. Halogen represented by R^{2c} means fluorine, chlorine, bromine and iodine and preferable group is bromine.

In the formula (I_y), C4-7 alkylene represented by R¹⁰⁰ means tetramethylene, pentamethylene, hexamethylene, heptamethylene and isomeric groups thereof.

In the formula (I_y), C4-7 alkenylene represented by R¹⁰⁰ means butenylen, pentenylen, hexenylen, heptenylen and isomeric groups thereof.

Preferable R¹⁰⁰ is pentamethylene, hexamethylene, pentenylen and hexenylen.

In the formula (I_y), C1-20 alkoxy represented by R²⁰⁰ means methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, pentadecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy and isomeric groups thereof.

In the formula (I_y), C1-4 alkyl represented by R²³⁰ and R²⁴⁰ means methyl, ethyl, propyl, butyl and isomeric groups thereof.

In the formula (I_y), amino acid residues represented by NR²³⁰N²⁴⁰ mean α-amino acid residues wherein a hydrogen in the amino is removed. For example, they are glycine, alanine, valine, isoleucine, leucine, serine, threonine, proline, asparagine, glutamine, methionine, phenylalanine, tyrosine, aspartic acid, glutamic acid or lysine residue.

In the formula (I_y), C1-4 alkylene represented by R³⁰⁰ means methylene, ethylene, trimethylene, tetramethylene and isomeric groups thereof.

Preferable R³⁰⁰ is a single bond and methylene.

In the formula (I_y), C1-4 alkyl represented by R⁴⁰⁰ means methyl, ethyl, propyl, butyl and isomeric groups thereof.

Preferable R⁴⁰⁰ is hydrogen and methyl.

In the formula (I_y), C1-4 alkyl represented by R⁶⁰⁰, R⁶¹⁰ and R⁶²⁰ means methyl, ethyl, propyl, butyl and isomeric groups thereof.

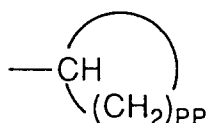
In the formula (I_y), C1-4 alkoxy represented by R⁶⁰⁰, R⁶¹⁰ and R⁶²⁰ means methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof.

In the formula (I_y), halogen represented by R⁶⁰⁰, R⁶¹⁰ and R⁶²⁰ means fluorine, chlorine, bromine and iodine.

Preferable R⁶⁰⁰, R⁶¹⁰ and R⁶²⁰ are hydrogen, fluorine, chlorine, bromine, iodine, methyl, methoxy, nitro and trifluoromethyl.

In the formula (I_y), the formula:

40



45

means cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and preferable group is cyclohexyl.

In the formula (I_y), C1-7 alkyl represented by R⁵⁰⁰ and R⁹⁰⁰ means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and isomeric groups thereof.

50 Preferable Compounds

In the compounds of the present invention of the formula (I_x), the compounds described in Example and the following compounds are preferable.

- 7-[3-(2-Naphtyl)sulfonylaminobicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
- 7-[3-(2-Cyclohexylethyl)sulfonylaminobicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
- 7-[3-Hexylsulfonylaminobicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
- 7-[5-(4-Methylphenyl)sulfonylaminobicyclo[2.2.1]-2-hepten-6-yl]-5-heptenoic acid,
- 7-[5-(2-Naphtyl)sulfonylaminobicyclo[2.2.1]-2-hepten-6-yl]-5-heptenoic acid,

7-[5-(2-Cyclohexylethyl)sulfonylaminobicyclo[2.2.1]-2-hepten-6-yl]-5-heptenoic acid,
 7-[5-Hexylsulfonylaminobicyclo[2.2.1]-2-hepten-6-yl]-5-heptenoic acid,
 7-[3-(4-Methylphenyl)sulfonylamino-7-oxa-bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-(2-Naphtyl)sulfonylamino-7-oxa-bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 5 7-[3-(2-Cyclohexylethylsulfonylamino)-7-oxa-bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-Hexylsulfonylamino-7-oxa-bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-(2-Naphtyl)sulfonylaminobicyclo[2.2.2]octan-2-yl]-5-heptenoic acid,
 7-[3-(2-Cyclohexylethyl)sulfonylaminobicyclo[2.2.2]octan-2-yl]-5-heptenoic acid,
 7-[3-Hexylsulfonylaminobicyclo[2.2.2]octan-2-yl]-5-heptenoic acid,
 10 7-[3-(4-Methylphenyl)sulfonylamino-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5-heptenoic acid,
 7-[2-(4-Methylphenyl)sulfonylaminocyclohexyl]-5-heptenoic acid,
 7-[2-(2-Naphtyl)sulfonylaminocyclohexyl]-5-heptenoic acid,
 7-[2-(2-Cyclohexylethyl)sulfonylaminocyclohexyl]-5-heptenoic acid,
 7-[2-Hexylsulfonylaminocyclohexyl]-5-heptenoic acid,
 15 7-[2-(2-Naphtyl)sulfonylaminocyclopentyl]-5-heptenoic acid,
 7-[2-(2-Cyclohexylethyl)sulfonylaminocyclopentyl]-5-heptenoic acid,
 7-[2-Hexylsulfonylaminocyclopentyl]-5-heptenoic acid,
 6-[3-(4-Methylphenyl)sulfonylaminocyclopentyl]-5-hexenoic acid,
 7-[3-(4-Methylphenyl)sulfonylaminocyclopentyl]-5-heptenoic acid,
 20 8-[3-(4-Methylphenyl)sulfonylaminocyclopentyl]-5,7-octadienoic acid,
 6-[3-(4-Methylphenyl)sulfonylaminocyclohexyl]-5-hexenoic acid,
 7-[3-(4-Methylphenyl)sulfonylaminocyclohexyl]-5-heptenoic acid,
 8-[3-(4-Methylphenyl)sulfonylaminocyclohexyl]-5,7-octadienoic acid,
 6-[6-(4-Methylphenyl)sulfonylaminobicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 25 7-[6-(4-Methylphenyl)sulfonylaminobicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 8-[6-(4-Methylphenyl)sulfonylaminobicyclo[2.2.1]heptan-2-yl]-5,7-octadienoic acid,
 6-[6-(4-Methylphenyl)sulfonylaminobicyclo[2.2.2]octan-2-yl]-5-hexenoic acid,
 7-[6-(4-Methylphenyl)sulfonylaminobicyclo[2.2.2]octan-2-yl]-5-heptenoic acid,
 8-[6-(4-Methylphenyl)sulfonylaminobicyclo[2.2.2]octan-2-yl]-5,7-octadienoic acid,
 30 6-[3-(4-Methylphenyl)sulfonylaminomethylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-(4-Methylphenyl)sulfonylaminomethylbicyclo[2.2.2]octan-2-yl]-5-hexenoic acid,
 6-[2-(4-Methylphenyl)sulfonylaminomethylcyclohexyl]-5-hexenoic acid,
 6-[5-(4-Methylphenyl)sulfonylaminomethylbicyclo[2.2.1]-2-hepten-6-yl]-5-hexenoic acid,
 6-[5-(4-Methylphenyl)sulfonylaminomethylbicyclo[2.2.2]-2-octen-6-yl]-5-hexenoic acid,
 35 6-[6-(4-Methylphenyl)sulfonylaminomethyl-3-cyclohexenyl]-5-hexenoic acid,
 6-[2-(4-Methylphenyl)sulfonylaminomethylcyclopentyl]-5-hexenoic acid,
 6-[3-(4-Methylphenyl)sulfonylaminomethyl-7-oxa-bicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 and ester, amido, amido with amino acid thereof.

In the compounds of the present invention of the formula (Iy), the compounds described in Example
 40 and the following compounds are preferable.

Esters, amides, amides with amino acid of example compounds,
 7-[3-[2-(4-Fluorophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(3-Fluorophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(4-Chlorophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 45 7-[3-[2-(3-Chlorophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(4-Bromophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(3-Bromophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(4-Iodophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(3-Iodophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 50 7-[3-[2-(4-Methylphenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(3-Methylphenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(4-Nitrophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(3-Nitrophenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(4-Methoxyphenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 55 7-[3-[2-(3-Methoxyphenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(4-Trifluoromethylphenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid
 7-[3-[2-(3-Trifluoromethylphenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,
 7-[3-[2-(2,2-diphenyl)vinylsulfonylamino]bicyclo[2.2.1]heptan-2-yl]-5-heptenoic acid,

- 6-[3-[2-(4-Fluorophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(3-Fluorophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(4-Chlorophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(3-Chlorophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 5 6-[3-[2-(4-Bromophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(3-Bromophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(4-Iodophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(3-Iodophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(4-Methylphenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 10 6-[3-[2-(3-Methylphenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(4-Nitrophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(3-Nitrophenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(4-Methoxyphenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(3-Methoxyphenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 15 6-[3-[2-(4-Trifluoromethylphenyl)vinylsulfonylamino]methylbicyclo[2.2.1] heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(3-Trifluoromethylphenyl)vinylsulfonylamino]methylbicyclo[2.2.1] heptan-2-yl]-5-hexenoic acid,
 6-[3-[2-(2,2-diphenyl)vinylsulfonylamino]methylbicyclo[2.2.1]heptan-2-yl]-5-hexenoic acid,
 7-[2-[2-(4-Fluorophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(3-Fluorophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 20 7-[2-[2-(4-Chlorophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(3-Chlorophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(4-Bromophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(3-Bromophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(4-Iodophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 25 7-[2-[2-(3-Iodophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(4-Methylphenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(3-Methylphenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(4-Nitrophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(3-Nitrophenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 30 7-[2-[2-(4-Methoxyphenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(3-Methoxyphenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(4-Trifluoromethylphenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(3-Trifluoromethylphenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 7-[2-[2-(2,2-diphenyl)vinylsulfonylamino]cyclohexyl]-5-heptenoic acid,
 35 6-[3-[2-(4-Fluorophenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 6-[3-[2-(3-Fluorophenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
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 6-[3-[2-(3-Chlorophenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
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 40 6-[3-[2-(3-Bromophenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
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 6-[3-[2-(3-Methylphenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 45 6-[3-[2-(4-Nitrophenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 6-[3-[2-(3-Nitrophenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 6-[3-[2-(4-Methoxyphenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 6-[3-[2-(3-Methoxyphenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 6-[3-[2-(4-Trifluoromethylphenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 50 6-[3-[2-(3-Trifluoromethylphenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 6-[3-[2-(2,2-diphenyl)vinylsulfonylamino]cyclohexyl]-5-hexenoic acid,
 6-[3-[2-(4-Fluorophenyl)vinylsulfonylamino]cyclopentyl]-5-hexenoic acid
 6-[3-[2-(3-Fluorophenyl)vinylsulfonylamino]cyclopentyl]-5-hexenoic acid,
 6-[3-[2-(4-Chlorophenyl)vinylsulfonylamino]cyclopentyl]-5-hexenoic acid,
 55 6-[3-[2-(3-Chlorophenyl)vinylsulfonylamino]cyclopentyl]-5-hexenoic acid,
 6-[3-[2-(4-Bromophenyl)vinylsulfonylamino]cyclopentyl]-5-hexenoic acid,
 6-[3-[2-(3-Bromophenyl)vinylsulfonylamino]cyclopentyl]-5-hexenoic acid,
 6-[3-[2-(4-Iodophenyl)vinylsulfonylamino]cyclopentyl]-5-hexenoic acid,

[illegible]

- [illegible]

6-[6-[2-(3-Trifluoromethylphenyl)vinylsulfonylamino]bicyclo[2.2.2]octan-2-yl]-5-hexenoic acid,
 6-[6-[2-(2,2-diphenyl)vinylsulfonylamino]bicyclo[2.2.2]octan-2-yl]-5-hexenoic acid,
 and ester, amido, amido with amino acid thereof.

The ester compounds, amide compounds and amide compounds with amino acid, themselves, have only weak pharmacological activities, but they show strong activities when an ester and amide bonds thereof are broken in the body after administration of them. They are what is called a prodrug.

Cyclodextrin clathrates

The cyclodextrin clathrates of the compounds of the formula (Ix) and (Iy) of the present invention may be prepared by the method described in the specification of the British Patent No. 1351238 or the British Patent No. 1419221, using α , β or γ -cyclodextrins or a mixture thereof.

By converting into cyclodextrin clathrates, the stability of the compounds of the formula (Ix) and (Iy) can be increased.

Salts

The compounds which R^{11} is hydrogen or $NR^{13}R^{14}$ is amino acid residue among the compounds of the formula (Ix), or R^{200} is hydroxy or $NR^{230}R^{240}$ is amino acid residue among the compounds of the formula (Iy), of the present invention may be converted into the corresponding salts. Non-toxic and water-soluble salts are preferable. Suitable salts, for example, are follows:

salts of alkaline metal (sodium, potassium etc.), salts of alkaline earth metal (calcium, magnesium etc.), ammonium salts, salts of pharmaceutically acceptable organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)aminomethane, lysine, arginine, N-methyl-D-glucamine etc.).

Process for the Preparation

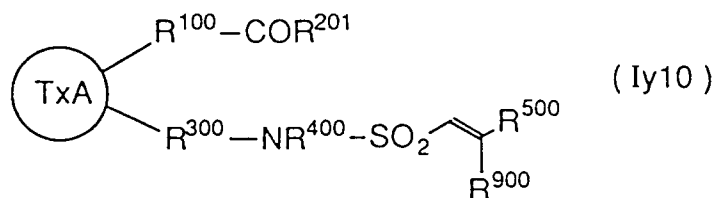
1) The compounds of the formula (Ix) are disclosed in the specification of the United States Patent No. 5168101 and the United States Patent No. 4861913, and the detailed processes for the preparation thereof are also disclosed therein.

The structures of unspecified compounds are described with physical data in example described hereafter in the present specification.

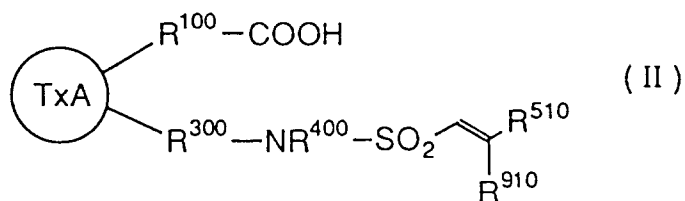
The compounds in which R^{3a} is benzene, naphthalene or C4-7 cycloalkyl substituted by trifluoromethyl, and in which R^{2b} or R^{2c} is C1-4 alkoxy, hydroxy, cyano, nitro or trifluoromethyl, in the compounds of the formula (Ix), may be also prepared by the same method as mentioned above.

2) The compounds of the formula (Iy) may be prepared as follows.

The compounds wherein R^{200} is R^{201} in which R^{201} is C1-20 alkoxy or $NR^{230}R^{240}$ (wherein all the symbols are the same meaning as hereinbefore defined), in the compounds of the formula (Iy), of the formula:

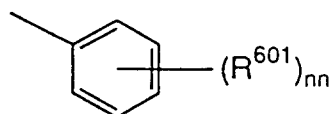


wherein all the symbols are the same meaning as hereinbefore defined, may be prepared from those of the formula:



10 wherein R⁵¹⁰ and R⁹¹⁰ each, independently, is

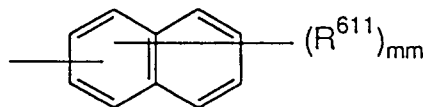
i)



20 in which R⁶⁰¹ is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro or 2-tetrahydropyranyloxy;

nn is the same meaning as hereinbefore defined;

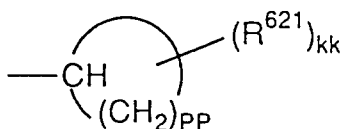
ii)



30 in which R⁶¹¹ is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro or 2-tetrahydropyranyloxy;

35 mm is the same meaning as hereinbefore defined;

iii)



45 in which R⁶²¹ is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro or 2-tetrahydropyranyloxy;

kk and pp are the same meaning as hereinbefore defined;

iv) C1-7 alkyl or

50 v) hydrogen,

and the other symbols are the same meaning as hereinbefore defined;

by the esterification reaction or the reaction of forming amide-bond, and by the hydrolysis in an acidic condition when R⁶⁰¹, R⁶¹¹ and R⁶²¹ is 2-tetrahydropyranyloxy.

The esterification reaction is known, for example, it may be carried out using (i) diazoalkane, (ii) a condensing agent (e.g. dicyclohexylcarbodiimide, Mukaiyama reagent etc.)

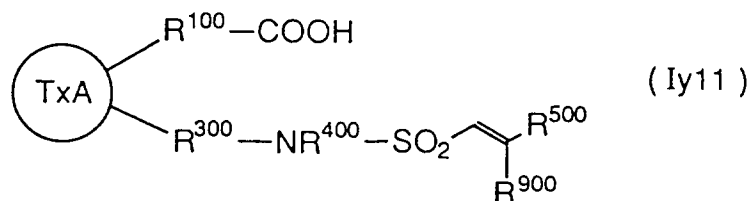
55 The method using diazoalkane of (i) is known, for example, it may be carried out using the corresponding diazoalkane, in an inert organic solvent (e.g. tetrahydrofuran (THF), dioxan, ether, acetone etc.) at -10 °C ~ 40 °C.

The method using a esterification agent of (ii) is known, for example, it may be carried out in an corresponding alkanol, using a condensing agent (dicyclohexylcarbodiimide, Mukaiyama reagent etc.) and tertiary amine (e.g. triethylamine etc.) at $-10^{\circ}\text{C}\sim 40^{\circ}\text{C}$.

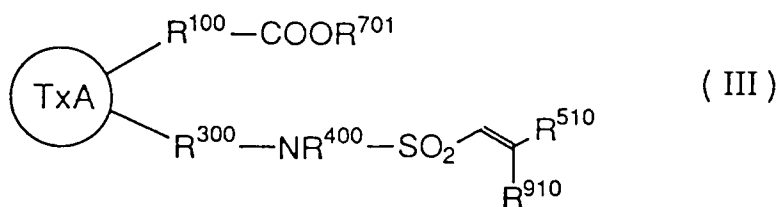
The reaction to forming amide-bond is known, for example, it may be carried out (i) with using a corresponding amine of the formula $\text{HNR}^{230}\text{R}^{240}$ wherein R^{230} and R^{240} are the same meaning as hereinbefore defined, in an inert organic solvent (e.g. methylene chloride, toluene etc.) at $0^{\circ}\text{C}\sim 40^{\circ}\text{C}$, after reacting oxalyl chloride, or (ii) with using a corresponding amine, Mukaiyama reagent and tertiary amine (e.g. triethylamine etc.), in an inert organic solvent (e.g. methylene chloride etc.), at $0^{\circ}\text{C}\sim 40^{\circ}\text{C}$. In case that an amine of the formula $\text{HNR}^{230}\text{R}^{240}$ is amino acid, the reaction is carried out by reacting the compounds in which carboxyl in an amino acid is protected by appropriate alkyl, or the compounds in which an amino having no connection to the reaction is protected by tert-butoxycarbonyl (boc) or benzyloxy carbonyl (cbz), and then hydrolyzing with using an acid (trifluoroacetic acid etc.) or an alkali (sodium hydroxide etc.) to remove a protecting group.

The hydrolysis of ester in an acidic condition is known, for example, it may be carried out in water-miscible organic solvent (e.g. methanol, ethanol, THF, dioxan etc.), using an organic acid (e.g. acetic acid, p-toluenesulfonic acid, trichloroacetic acid etc.) or an inorganic acid (e.g. hydrochloride, sulfate, hydrobromide etc.) at $0^{\circ}\text{C}\sim 90^{\circ}\text{C}$.

The compounds which R^{200} is hydroxy in the compounds of the formula (Iy), of the formula:



wherein all the symbols are the same meaning as hereinbefore defined; may be prepared from those of the formula:



wherein R^{701} is C1-4 alkyl and the other symbols are the same meaning as hereinbefore defined ; by the hydrolysis in an alkaline condition, and by the hydrolysis in an acidic condition when R^{601} , R^{611} and R^{621} is 2-tetrahydropyranyloxy.

The hydrolysis of ester in an alkaline condition is known, for example, it may be carried out in a water-miscible organic solvent (e.g. THF, methanol, ethanol dimethoxyethane or mixture thereof etc.), using an alkali (e.g. sodium hydroxide, potassium hydroxide etc.), at $-10^{\circ}\text{C}\sim 100^{\circ}\text{C}$.

The hydrolysis of ester in an acidic condition may be carried out the same procedure as mentioned above.

Besides, the procedure of this two reactions may be carried out reversibly.

The compounds of the formula (II) may be prepared from those of the formula (III) by the hydrolysis in an alkaline condition.

The hydrolysis of ester in an alkaline condition may be carried out the same procedure as mentioned above.

The compounds of the formula (III) may be prepared by using a reaction depicted in following Scheme (A).

The reaction step in parenthesis may be carried out, if desired.

The symbols in scheme is the following meaning or the same meaning as hereinbefore defined.

THP : 2-tetrahydropyranyl,

R¹⁰¹ : a single bond or C1-4 alkylene,

R¹⁰² : C1-5 alkylene,

5 R⁸¹⁰ : t-butoxycarbonyl,

R⁴⁰¹ : C1-4 alkyl,

X¹⁰ : halogen,

X²⁰ : halogen,

X³⁰ : halogen,

10 X⁴⁰ : halogen,

φ : phenyl

TsOH : p-toluenesulfonic acid

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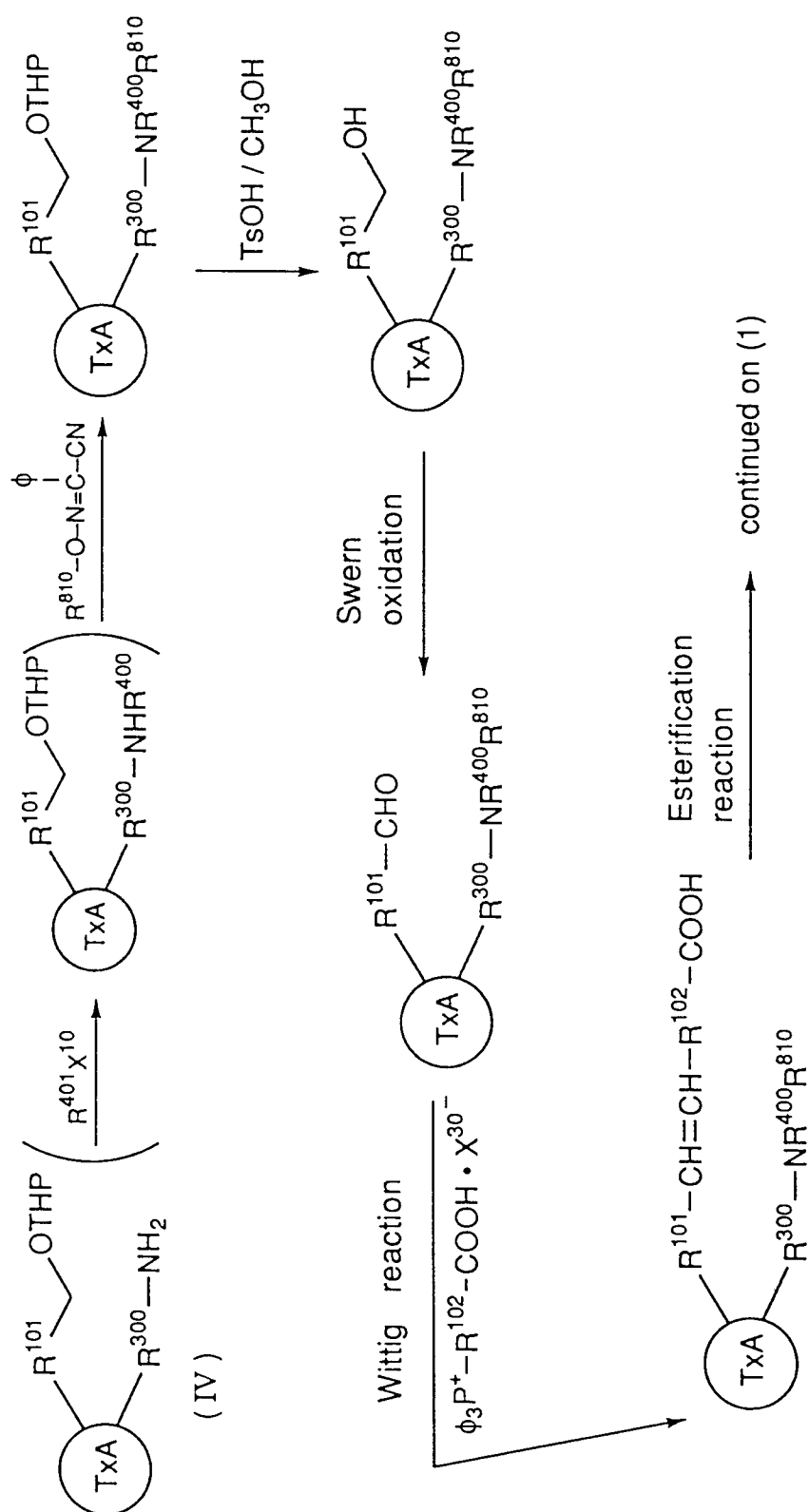
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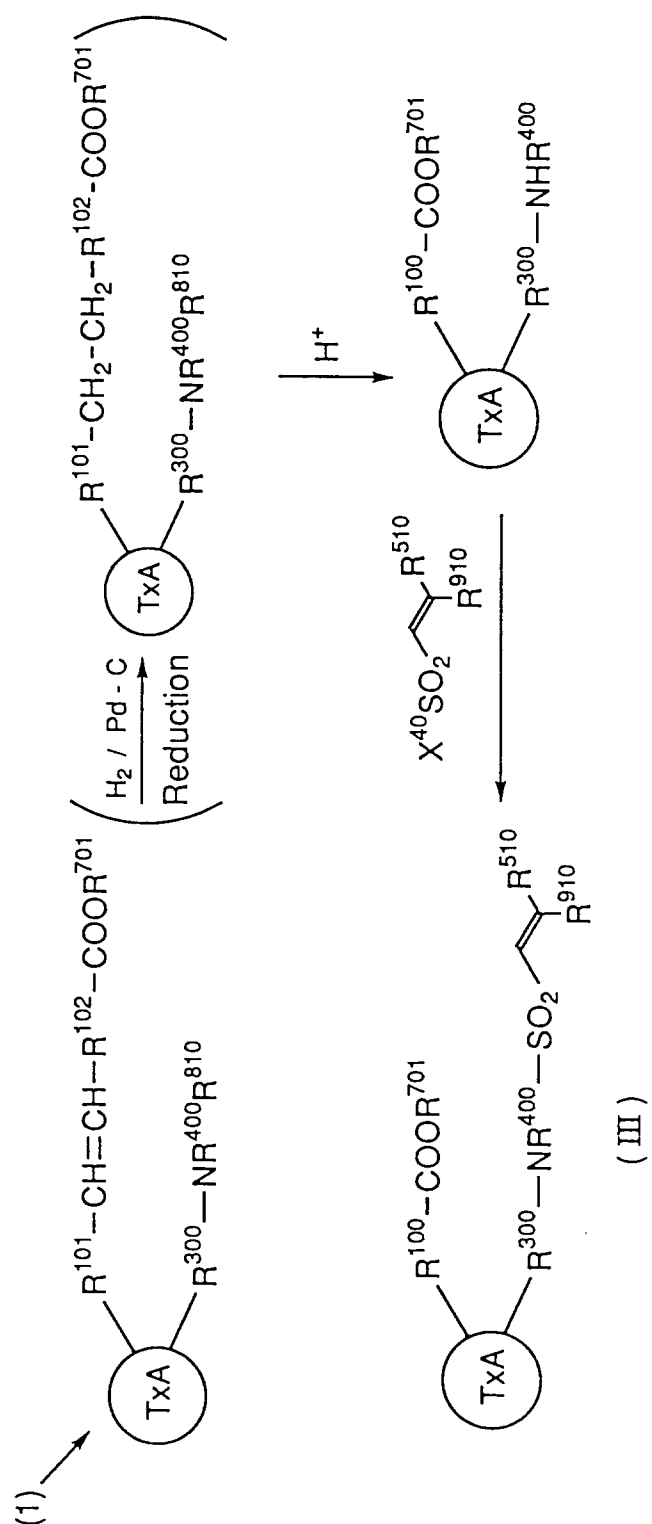
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Scheme (A)



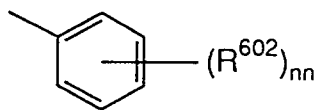
Scheme (A) (continued)



In the formula (Iy), the compounds in which R^{100} is C4-7 alkenylene, R^{200} is hydroxy, R^{500} is R^{501} , wherein R^{501} is

i)

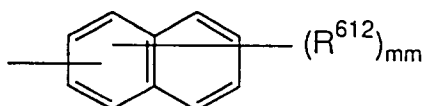
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in which R^{602} is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl or nitro, nn is the same meaning as hereinbefore defined, or
ii)

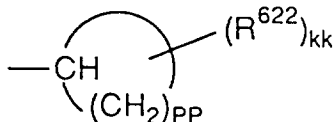
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in which R^{612} is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl or nitro, mm is the same meaning as hereinbefore defined, or
iii)

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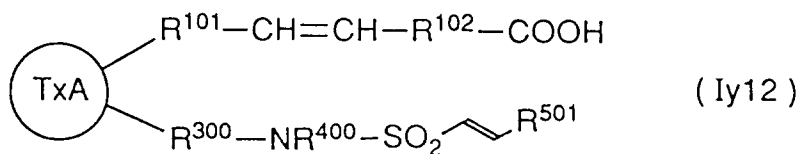


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in which R^{622} is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl or nitro, kk and pp are the same meaning as hereinbefore defined, or
iv) C1-7 alkyl
and R^{900} is hydrogen;
of the formula:

35

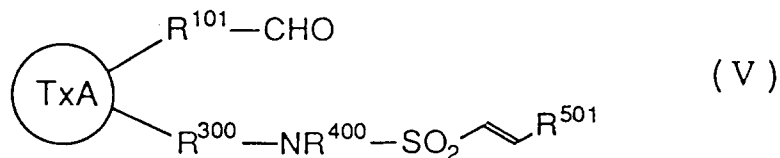
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wherein all the symbols are the same meaning as hereinbefore defined;
may be prepared by subjecting the compound of the formula:

50



55

wherein all the symbols are the same meaning as hereinbefore defined;
and the compound of the formula:



wherein X^{40} is halogen, ϕ is phenyl, R^{102} is the same meaning as hereinbefore defined;
to Wittig reaction.

5 Wittig reaction is known, for example, it may be carried out by reacting the phosphonium salt mentioned above in an inert organic solvent (e.g. toluene, THF, dimethylsulfoxide (DMSO) etc.), in the presence of a strong base (e.g. potassium tert-butoxide, lithium diisopropylamide, sodium hydroxide etc.), at -78°C to room temperature.

10 The compounds of the formula (V) may be prepared by using a reaction depicted in following Scheme (B).

The reaction step in parenthesis may be carried out, if desired.

The symbols in scheme is the following meaning or the same meaning as hereinbefore defined.

15 X^{50} : halogen,
Me : methyl,
Et₃N : triethylamine,
n-BuLi: n-butyl lithium

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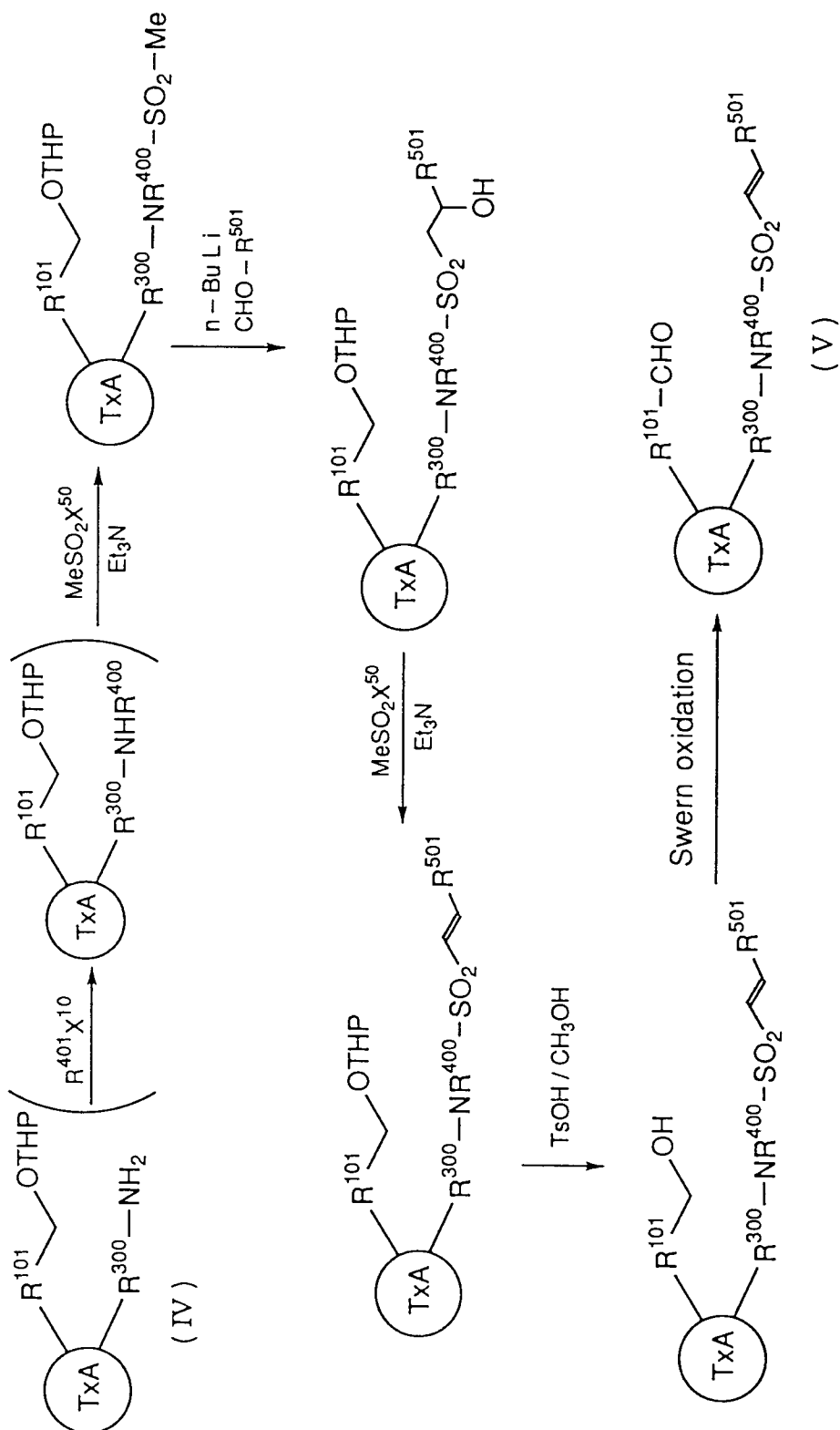
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Scheme (B)



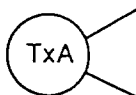
As mentioned above, the compounds of the present invention contain various optical isomers due to asymmetric carbon(s) thereof. However, when a single or a specific optically active substance is desired, it may be prepared by using a compound having the desired optical activity as a starting material, or by resolving into each optically active substance at a preferable step by means such as optical resolution etc.

Starting materials and reagents

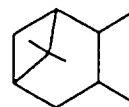
The starting materials and reagents in the present invention are known per se or may be prepared by known methods.

5 For example, the compound which

10



is



15 in the compounds of the formula (IV) is described in specification of the United States Patent No. 4861913 and the United States Patent No. 5168101.

Pharmacological Activities

20 The compounds of the present invention of the formula (Ix) and (Iy) are useful for PGE₂ antagonists or agonists, because they bind onto prostaglandin E₂ receptor and have an activity of antagonist or agonist against the action thereof. PGE₂ antagonists are expected to inhibit an uterine contraction, to have an analgetic action, to inhibit a digestive peristalsis, to induce a sleep. PGE₂ agonists are expected to contractile an uterine, to promote a digestive peristalsis, to suppress a gastric acid secretion, to low a blood pressure.

25 For example, in standard laboratory test, the effects were confirmed by (i) the Inhibitory effects of [³H]-PGE₂ receptor binding in rat uterus membrane fraction, (ii) the inhibitory effects of rat uterine contraction induced by PGE₂.

The results of the experiments are shown in the table I and table II.

(i) The measurement of the inhibition of [³H]-PGE₂ receptor binding

30 The standard assay mixture contained 5nM [³H]-PGE₂ (50μl), test compounds (50μl) and crude membrane fraction obtained from rat uterus (1.2 mg protein/ml, 100μl) in a final volume of 200μl (10 mM potassium phosphate pH 6.0, 0.1 M NaCl (buffer A)). After incubation for 1 hour at room temperature, the reaction was stopped by the addition of 3 ml of ice-cold buffer A, after which the mixture was rapidly filtered through a Whatman GF/B glass filter. The radioactivity associated with the filter was measured in
35 ACS II (Amarsham) by liquid scintillation counting. Percent inhibition of specific [³H]-PGE₂ binding or IC₅₀ value, the concentration required to compete with ³H-PGE₂ receptor binding by 50% were calculated.

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table I: Inhibitory effects of PGE₂ receptor binding in rat

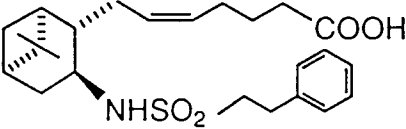
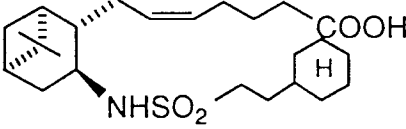
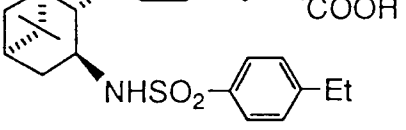
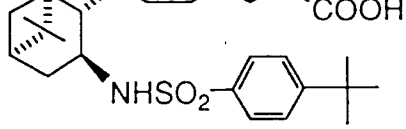
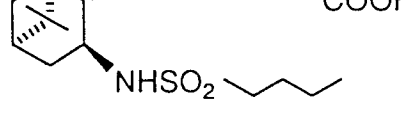
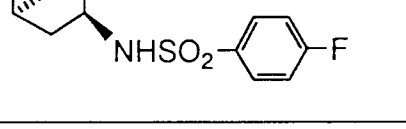
Structure	Ex. No.	IC ₅₀ (μM)
	3 (m)	0.0054
	3 (n)	0.12
	3 (b)	0.57
	3 (c)	6.3
	3 (j)	5.0
	3 (e)	2.6

table I (continued)

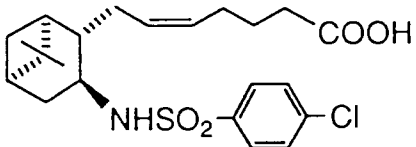
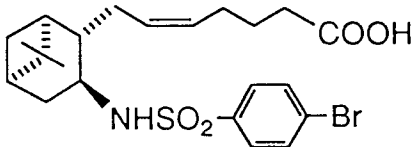
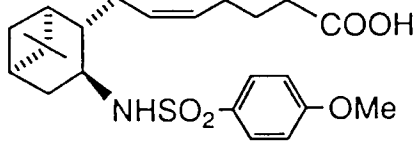
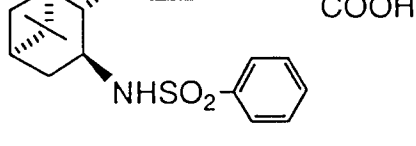
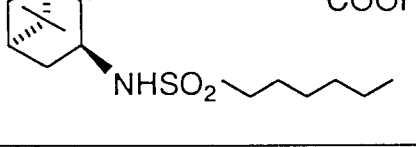
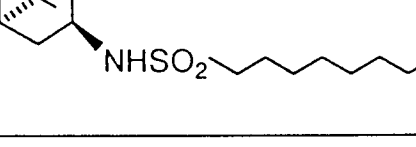
Structure	Ex. No.	IC ₅₀ (μM)
	3 (f)	0.75
	2	0.44
	3 (d)	0.82
	3 (a)	7.6
	3 (k)	0.025
	3 (l)	0.36

table I (continued)

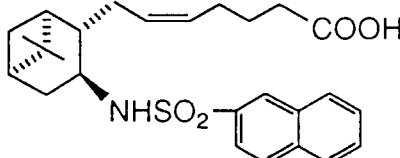
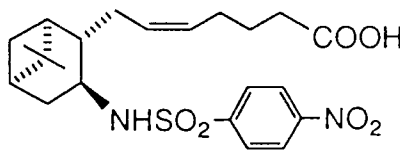
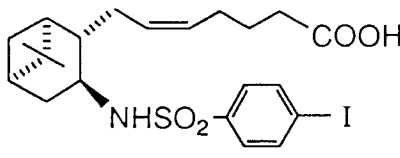
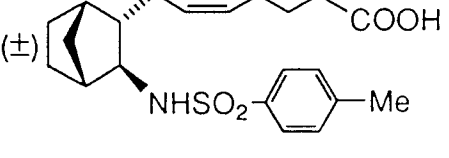
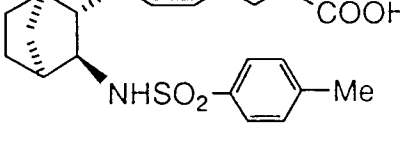
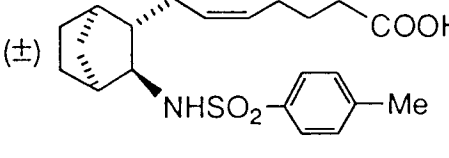
Structure	Ex. No.	IC ₅₀ (μM)
	3 (i)	0.09
	3 (h)	0.21
	3 (g)	0.054
	5 (b)	3.4
	4	3.4
	5 (c)	5.7

table I (continued)

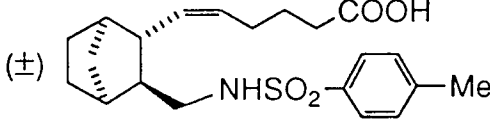
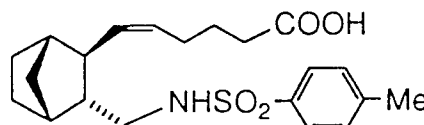
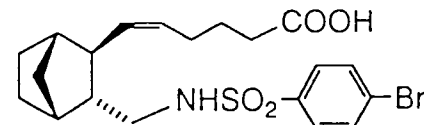
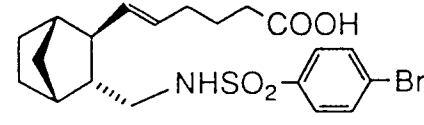
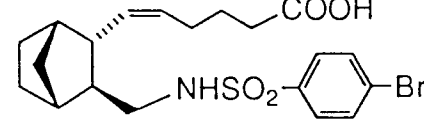
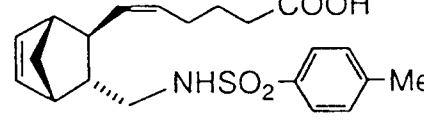
Structure	Ex. No.	IC ₅₀ (μM)
10 15 (±) 	United States Patent No. 5168101 1 (p)	6.4
20 	United States Patent No. 5168101 1 (x)	1.6
25 	United States Patent No. 5168101 1 (y)	0.62
30 35 	United States Patent No. 5168101 1 (cc)	0.39
40 	5 (i)	6.5
45 50 	United States Patent No. 5168101 1 (aa)	2.0

table I (continued)

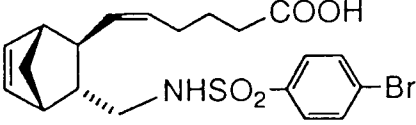
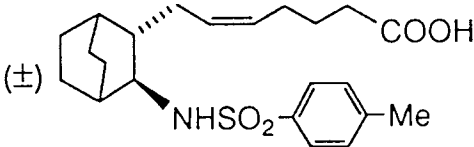
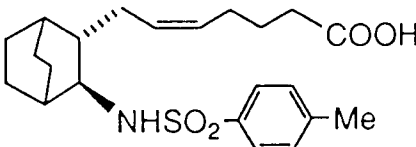
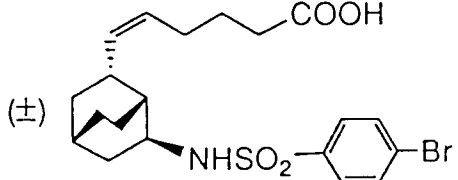
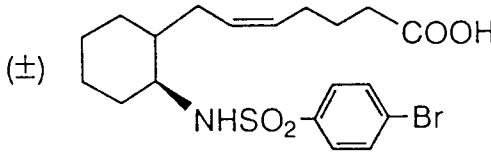
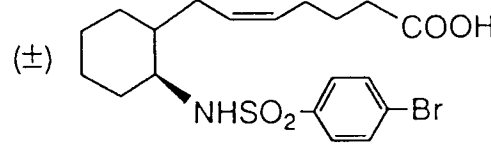
Structure	Ex. No.	IC ₅₀ (μM)
	United States Patent No. 5168101 1 (bb)	0.82
	5 (a)	3.6
	5 (d)	2.1
	United States Patent No. 5168101 1 (a)	0.77
 <p>more polar</p>	5 (e)	0.06
 <p>less polar</p>	5 (f)	5.0

table I (continued)

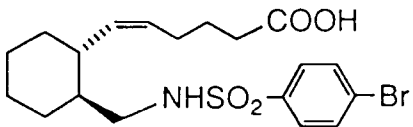
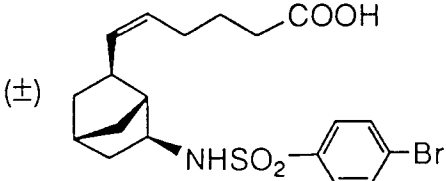
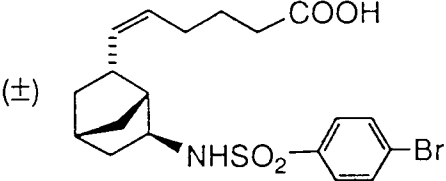
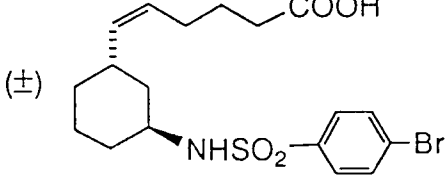
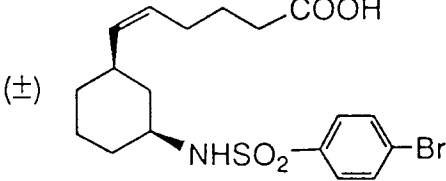
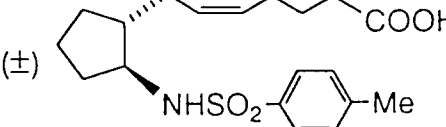
Structure	Ex. No.	IC ₅₀ (μM)
	United States Patent No. 5168101 1 (t)	1.2
	United States Patent No. 5168101 1 (b)	3.5
	United States Patent No. 5168101 1 (c)	0.5
	United States Patent No. 5168101 1 (l)	2.4
	United States Patent No. 5168101 1 (m)	0.5
	5 (g)	3.5

table I (continued)

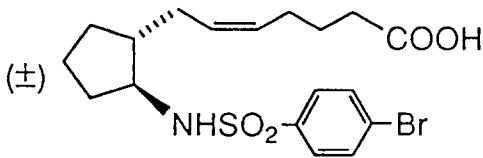
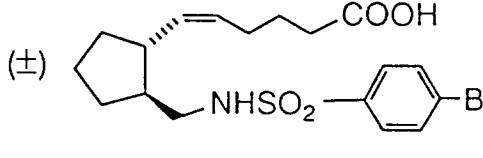
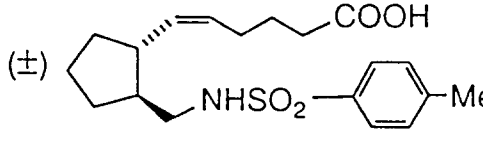
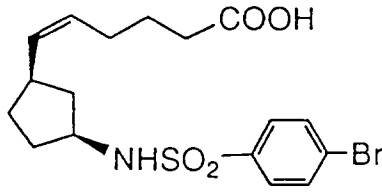
Structure	Ex. No.	IC ₅₀ (μM)
(±) 	5 (h)	0.2
(±) 	European Patent Publication No. 0312906 1 (v)	1.8
(±) 	European Patent Publication No. 0312906 1 (w)	8.0
	United States Patent No. 5168101 1 (i)	2.4

table II: Inhibitory effects of PGE₂ receptor binding in rat

Structure	Ex. No.	IC ₅₀ (μM)
	6 (2)	0.0036
	6 (14)	0.8
	6 (12)	< 0.01
	6 (18)	0.017
	6 (19)	0.23
	6 (21)	0.6
	6 (22)	1.8
	6 (26)	0.038
	9	0.26

(ii) The inhibitory effects of compounds on contraction of rat uterus induced by PGE₂

Pseudo pregnant rat uterus (Sprague Dawley, 200-300 g, induced by oestradiol 500 μg/kg s.c. 18-24 hours before experiment) was isolated and longitudinal strips of 1-1.5cm were set up in Locke-Ringer solution containing low Ca²⁺, aerated with mixed gas (oxygen 95% + carbon dioxide 5%) at 28°C. A resting tension of 1 g was imposed on the tissue and contraction were recorded isometrically and

displayed on recticorder.

The compound of example 6(12) was completely inhibited the contraction induced by 0.3 μ M PGE₂.

Toxicity

5

The toxicity of the compound of the present invention of the formula (Ix) and (Iy) are very low and therefore, it may be estimated to safe for pharmaceutical use.

For example, the acute toxicity (LD₅₀) in mouse of 6-[(1S, 2R, 3R, 4R)-3-(4-bromophenylsulfonylaminomethyl)bicyclo[2.2.1]heptan-2-yl]-5Z-hexenoic acid (it is described as example 1(y) in specification of the United States Patent No. 5168101.) was more than 300 mg/kg by oral administration.

10

Application for Pharmaceuticals

The compounds of the present invention of the formula (Ix) and (Iy), cyclodextrin clathrates thereof and non-toxic salts thereof, are useful for PGE₂ antagonists or agonists, because they bind onto prostaglandin E₂ receptor and have an activity of antagonist or agonist against the action thereof.

15

PGE₂ antagonists are considered to inhibit an uterine contraction, to have an analgetic action, to inhibit a digestive peristalsis, to induce a sleep, therefor they are useful for prevention and/or treatment of abortion, pain, diarrhea, insomnia.

20

PGE₂ agonists are considered to contractile an uterine, to promote a digestive peristalsis, to suppress a gastric acid secretion, to low a blood pressure, therefor they are useful for prevention and/or treatment of constipation, ulcer, gastritis, hypertensive, and for induction of labour in pregnant female mammals.

For the purpose above described, the compounds of the formula (Ix) and (Iy), of the present invention and cyclodextrin clathrates thereof and non-toxic salts thereof may be normally by administered systemically or partially usually by oral or parenteral administration.

25

The doses to be administered is determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person per dose are generally between 0.01 mg and 0.1 mg, by oral administration up to several times per day, and between 1 μ g and 100 μ g, by parenteral administration up to several times per day. As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

30

Solid compositions according to the present invention for oral administration include compressed tablets, dispersible powders and granules. In such solid compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate. The compositions may also comprise, as is normal practice, additional substances other than inert diluents e.g. lubricating agents such as magnesium stearate, disintegrating agents such as cellulose calcium glycolate, stabilizing agent e.g. lactose and assistant for dissolving e.g. arginine, glutamic acid or aspartic acid. The tablets or pills may, if desired, be made into gastric film-coated or enteric film-coated tablets or pills, such as sugar-coated, gelatin-coated, hydroxypropyl cellulose-coated or hydroxypropylmethyl cellulose phthalate-coated tablets or pills; two or more of layers may be used. The compositions for oral administration also include capsules of absorbable material such as gelatin.

35

40

Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as distilled water or ethanol. Besides inert diluents such compositions may also comprise adjuvants such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents.

45

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s).

Preparations for injection according to the present invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions or emulsions. Example of aqueous solvents or suspending media are distilled water for injection and physiological salt solution. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol, POLYSORBATE 80 (registered Trade Mark). These compositions may also include adjuvants such as preserving, wetting, emulsifying, dispersing agents, stabilizing agents (e.g. lactose) and assistant agent for dissolving (e.g. arginine, glutamic acid or aspartic acid). They may also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

50

55

Other compositions for parenteral administration include liquids for external use, and endermic liniments such as ointments, suppositories for rectal administration and pessaries for vaginal administration which comprise one or more of the active compound(s) and may be prepared by known methods.

5 Reference examples and Examples

The following reference examples and examples illustrate the present invention, but not limit the present invention.

In the reference examples and examples, "TLC", "NMR", "IR" and "MS" represent "Thin layer chromatography", "Nuclear magnetic resonance spectrum", "Infrared absorption spectrum" and "Mass spectrum", respectively.

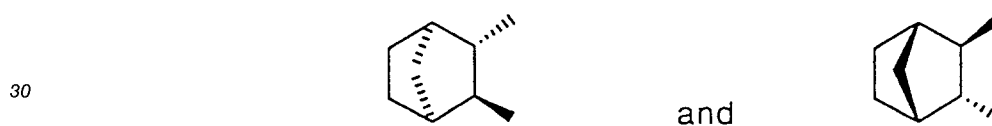
The solvents in the parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations.

Unless otherwise specified, "NMR" was measured in a chloroform-d (CDCl_3) solution and "IR" was measured by the liquid film method respectively.

And (\pm) in reference examples and examples represent the mixture of enantiomers having different angles of rotation as generally used in the nomenclature. For example,



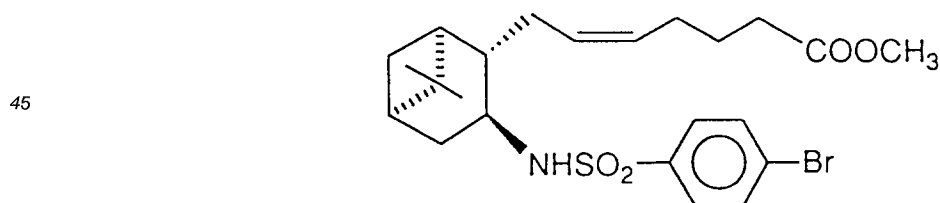
25 represents the mixture of



35 and * are added to indications of absolute configuration at the same time.

Example 1

40 7-[(1S,2S,3S,5R)-3-(4-bromophenyl)sulfonylamino-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid methyl ester



50

A solution of 7-[(1S,2S,3S,5R)-3-amino-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid methyl ester (the compound was described as reference example 14 in specification of the United States Patent No. 4792550.) (140 mg) in pyridine (5 ml) was cooled with ice-bath. A solution of 4-bromobenzenesulfonyl chloride (153 mg) in methylene chloride (2 ml) was dropped to the above solution. The mixture was stirred for 16 hours at room temperature. The reaction mixture was poured into 4N hydrochloric acid (30 ml) and extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate and brine,

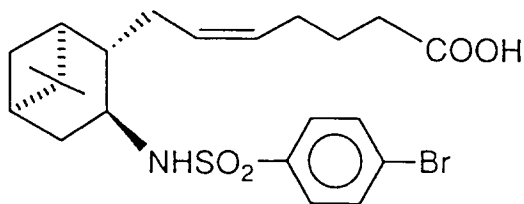
successively, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 6) to give the title compound (155 mg) having the following physical data.

NMR: δ 7.77 (2H, d), 7.64 (2H, d), 5.29 (2H, m), 4.62 (2H, d), 3.70 (3H, s), 3.59 (1 H, m), 2.30 (2H, t), 1.18 (3H, s), 0.95 (3H, s), 0.76 (1H, d);

MS: m/e 497 (M^+), 499, 466, 468, 428, 430, 401, 403, 396, 398.

Example 2

7-[(1S,2S,3S,5R)-3-(4-bromophenyl)sulfonylamino-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid



To a solution of the methyl ester compound prepared in example 1 (60 mg) in methanol (6 ml), 10% sodium hydride solution (2 ml) was added. The mixture was stirred for 5 hours at room temperature. After methanol was distilled off from the reaction mixture, ice and 3N hydrochloric acid (20 ml) were added to the residue. The above solution was extracted with ethyl acetate (three times). The extract was dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (53 mg) having the following physical data.

TLC: Rf 0.45 (methylene chloride : methanol = 10 : 1);

NMR: δ 7.77 (2H, td), 7.65 (2H, td), 5.50~5.24 (3H, m), 3.63(1H, m), 2.43-1.42 (14H), 1.17 (3H, s), 0.94 (3H, s), 0.76 (1H, d);

MS: m/e 483 (M^+), 465, 414, 396;

Feature: pale yellow amorphous.

Example 3

By the same procedure as in example 1→example 2, using 7-[(1S, 2S,3S,5R)-3-amino-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid methyl ester (the compound was described as reference example 14 in specification of the United States Patent No. 4792550.) and various sulfonyl compounds as starting material, purposed compounds shown in following table were given.

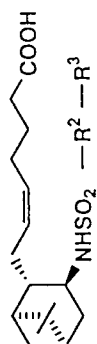


table III


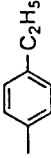

Example No.	$-R^2-R^3$	Name	TLC (Rf)	NMR (δ)	MS (m/e)	Feature
3 (a)		7-[(1S,2S,3S,5R)-3-phenyl sulfonylamino-6,6-dimethyl bicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.50 (methylene chloride : methanol = 10:1)	7.92(2H, m), 7.55(3H, m), 5.34(3H, m), 3.66(1H, m), 2.40~1.44(14H), 1.16(3H, s), 0.94(3H, s), 0.79(1H, d)	405(M ⁺), 387, 336, 318	pale yellow wax
3 (b)		7-[(1S, 2S, 3S, 5R)-3-(4-ethylphenyl)sulfonylamino-6, 6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid	0.50 (methylene chloride : methanol = 10:1)	7.80(2H, d), 7.31(2H, d), 5.35(2H, m), 5.16(1H, d), 3.62(1H, m), 2.71(2H, q), 2.35(2H, t), 2.30~1.40(13H, m), 1.24(3H, t), 1.16(3H, s), 0.94(3H, s), 0.76(1H, d)	433(M ⁺), 415, 364, 346, 337, 238, 237	pale yellow oil
3 (c)		7-[(1S, 2S, 3S, 5R)-3-(4-tert-butylphenyl)sulfonylamino-6, 6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid	0.50 (methylene chloride : methanol = 10:1)	7.80(2H, dt), 7.48(2H, dt), 5.32(2H, m), 5.12(1H, broad), 3.63(1H, broad), 2.35(2H, t), 2.30~1.40(13H), 1.34(9H, s), 1.16(3H, s), 0.94(3H, s), 0.76(1H, d)	461(M ⁺), 443, 392, 374, 365, 294	pale yellow wax

table III (continued)

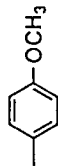
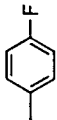
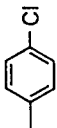
Example No.	$-R^2-R^3$	Name	TLC (R _f)	NMR (δ)	MS (m/e)	Feature
3 (d)		7-[(1S, 2S, 3S, 5R)-3-(4-methoxyphenyl)sulfonylamino-6, 6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.50 (methylene chloride : methanol = 10:1)	7.82(2H, dt), 6.96(2H, dt), 5.38(2H, m), 5.00(1H, broad), 3.85(3H, s), 3.58(1H, m), 2.40~1.40(14H, s), 0.93(3H, s), 0.76(1H, d)	435(M ⁺), 417, 366, 348, 339	colorless wax
3 (e)		7-[(1S, 2S, 3S, 5R)-3-(4-fluorophenyl)sulfonylamino-6, 6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.45 (methylene chloride : methanol = 10:1)	7.92(2H, dd), 7.18(2H, t), 5.38(3H, m), 3.62(1H, broad), 2.42~1.40(14H), 1.18(3H, s), 0.95(3H, s), 0.76(1H, d)	423(M ⁺), 405, 354, 336	colorless wax
3 (f)		7-[(1S, 2S, 3S, 5R)-3-(4-chlorophenyl)sulfonylamino-6, 6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.45 (methylene chloride : methanol = 10:1)	7.84(2H, dt), 7.48(2H, dt), 5.40(3H, m), 3.62(1H, broad), 2.42~1.40(14H), 1.18(3H, s), 0.95(3H, s), 0.76(1H, d)	439(M ⁺), 421, 398, 370, 352, 272	pale yellow wax

table III (continued)

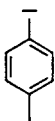
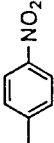
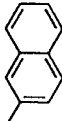
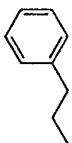
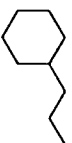
Example No.	$\text{---R}^2\text{---R}^3$	Name	TLC (Rf)	NMR (δ)	MS (m/e)	Feature
3 (g)		7-[(1S, 2S, 3S, 5R)-3-(4-iodophenyl)sulfonylamino-6, 6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.45 (methylene chloride : methanol = 10:1)	7.85(2H, dt), 7.60(2H, dt), 5.35(2H, m), 5.23(1H, d), 3.61(1H, m), 2.40~1.40(14H), 1.16(3H, s), 0.93(3H, s), 0.76(1H, d)	531(M ⁺), 513, 463, 444, 425	white solid
3 (h)		7-[(1S, 2S, 3S, 5R)-3-(4-nitrophenyl)sulfonylamino-6, 6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.40 (methylene chloride : methanol = 10:1)	8.34(2H, dt), 8.08(2H, dt), 5.49(1H, d), 5.36(2H, m), 3.79(1H, m), 2.40~1.40(14H), 1.08(3H, s), 0.94(3H, s), 0.76(1H, d)	450(M ⁺), 432, 331, 363	white wax
3 (i)		7-[(1S, 2S, 3S, 5R)-3-(2-naphthyl)sulfonylamino-6, 6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.55 (methylene chloride : methanol = 10:1)	8.46(1H, d), 7.92(4H, m), 7.62(2H, m), 5.30(3H, m), 3.68(1H, m), 2.40~1.44(14H), 1.14(3H, s), 0.92(3H, s), 0.78(1H, d)	455(M ⁺), 437, 414, 386, 368, 359	white solid

table III (continued)

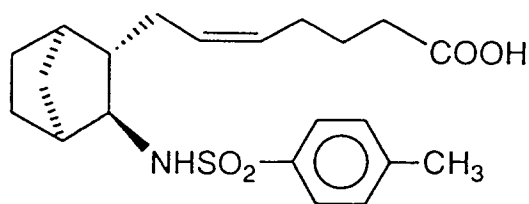
Example No.	$-\text{R}^2-\text{R}^3$	Name	TLC (Rf)	NMR (δ)	MS (m/e)	Feature
3 (j)	$-(\text{CH}_2)_3\text{CH}_3$	7-[(1S, 2S, 3S, 5R)-3-butyl sulfonfylamino-6, 6-dimethyl bicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.50 (methylene chloride : methanol = 10:1)	5.42(2H, m), 5.00(1H, broad), 3.72(1H, broad), 3.01(2H, dt), 2.70~1.35(18H), 1.21(3H, s), 1.02(3H, s), 0.94(3H, t), 0.83(1H, d)	385(M ⁺), 367, 316, 298	pale yellow oil
3 (k)	$-(\text{CH}_2)_5\text{CH}_3$	7-[(1S, 2S, 3S, 5R)-3-hexyl sulfonfylamino-6, 6-dimethyl bicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.45 (methylene chloride : methanol = 10:1)	5.46(2H, m), 4.94(1H, d), 3.72(1H, m), 3.02(2H, m)	413(M ⁺), 395, 334, 326	pale yellow oil
3 (l)	$-(\text{CH}_2)_7\text{CH}_3$	7-[(1S, 2S, 3S, 5R)-3-octyl sulfonfylamino-6, 6-dimethyl bicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.45 (methylene chloride : methanol = 10:1)	5.42(2H, m), 3.72(1H, m), 3.00(2H, m)	441(M ⁺), 423, 372, 354	pale yellow oil

table III (continued)

Example No.	$-R^2-R^3$	Name	TLC (Rf)	IR (ν cm^{-1})
3 (m)		7-[(1S,2S,3S,5R)-3-(2-phenylethyl)sulfonyl amino-6, 6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.24 (ethyl acetate : hexane = 1:1)	3272, 1708, 1604, 1455, 1306, 1236, 1147, 1062
3 (n)		7-[(1S,2S,3S,5R)-3-(2-cyclohexylethyl)sulfonyl amino-6, 6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.25 (ethyl acetate : hexane = 2:3)	3271, 2926, 1708, 1450, 1309

Example 4

7-[(1R,2S,3S,4S)-3-tosylaminobicyclo[2.2.1]heptan-2-yl]-5Z-heptenoic acid



Potassium tert-butoxide (740 mg) was added to a suspension 4-carboxybutyltriphenylphosphonium bromide (1.33 g) in toluene (10 ml). The mixture was stirred for 40 minutes at 80 °C. The reaction solution was cooled at 0 °C. A solution of [(1R,2S,3S,4S)-3-tosylaminobicyclo[2.2.1]heptan-2-yl]acetaldehyde (the compound was described as reference example 20 in specification of the United States Patent No. 5168101) (270 mg) in toluene (10 ml) was dropped to the reaction solution. The mixture was stirred for 15 minutes at 0 °C. The reaction mixture was poured into ice-water and extracted with ether. The water layer was acidified by adding 1N hydrochloric acid (10 ml) and extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride : methanol = 25:1) to give the title compound (222 mg) having the following physical data.

TLC: Rf 0.45 (methylene chloride : methanol = 10:1);

NMR: δ 7.75(2H, d), 7.28(2H, d), 5.26(2H, m), 5.11(1H, d), 3.00(1H), 2.42(3H, s), 2.37(2H, t), 2.16~0.87(15H);

MS: m/e 391(M⁺), 373;

Feature: white powder.

Example 5

By the same procedure as in example 4, using corresponding starting materials and various phosphonium salts, purposed compounds shown in following table IV and table V were given.

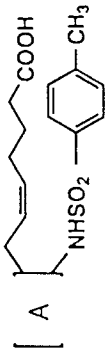






table IV

Example No.		Name	TLC (Rf)	NMR (δ)	MS (m/e)	Feature
5 (a)	 (±)	7-[(2S*,3S*)-3-tosylamino bicyclo[2.2.2]octan-2-yl]-5Z-heptenoic acid	0.45 (methylene chloride : methanol = 10:1)	7.75(2H, d), 7.26(2H, d), 5.28(3H, m), 2.86(1H, t), 2.42(3H, s), 2.37(2H, t), 2.20~1.10(17H)	405(M ⁺), 387, 361	white wax
5 (b)	mixture of  and 	a mixture of 7-[(1R, 2S, 3S, 4S)-3-tosylaminobicyclo[2.2.1]heptan-2-yl]-5Z-heptenoic acid and an isomer of (1S, 2S, 3S, 4R)	0.45 (methylene chloride : methanol = 10:1)	7.74(2H, d), 7.28(2H, d), 5.28(2H, m), 5.15(1H, d), 3.00(1H, m), 2.43(3H, s), 2.35(2H, t), 2.16~0.87(15H)	391(M ⁺), 373, 363, 345, 289	colorless oil

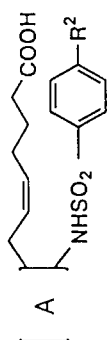


table V

Example No.	A, R ²	Name	TLC (R _f)	IR (ν cm ⁻¹)
5 (c)		7-[(1R*, 2S*, 3S*, 4S*)-3-tosylamino bicyclo[2.2.1]heptan-2-yl]-5Z-heptenoic acid	0.45 (methylene chloride : methanol = 10:1)	3270, 2950, 1705, 1600, 1420, 1320, 1150, 1090, 815
5 (d)		7-[(2S, 3S)-3-tosylaminobicyclo[2.2.2]octan-2-yl]-5Z-heptenoic acid	0.50 (methylene chloride : methanol = 10:1)	(solution of chloroform) 3270, 2950, 1720, 1420, 1330, 1170, 1105
5 (e)		7-[2-(4-bromophenylsulfonylamino) cyclohexyl]-5Z-heptenoic acid more polar	0.42 (methylene chloride : methanol = 9:1)	(KBr disk method) 3280, 2920, 1690, 1430, 1330, 1155, 1080, 1065

table V (continued)


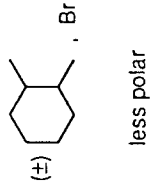
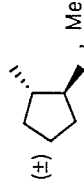
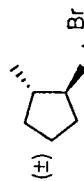
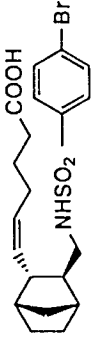
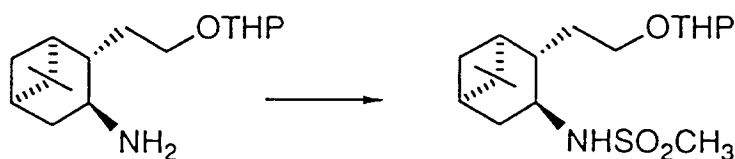
Example No.	 A, R ²	Name	TLC (R _f)	IR (ν cm ⁻¹)
5 (f)	 (±) less polar	7-[2-(4-bromophenyl)sulfonylamino]cyclohexyl]-5Z-heptenoic acid	0.42 (methylene chloride : methanol = 9:1)	(KBr disk method) 3280, 2920, 1690, 1430, 1330, 1155, 1080, 1065
5 (g)	 (±)	7-[(1R*, 2S*)-2-tosylaminocyclopentyl]-5Z-heptenoic acid	0.20 (ethyl acetate : hexane = 1:1)	3260, 2940, 1705, 1600, 1430, 1320, 1155, 1095, 910
5 (h)	 (±)	7-[(1R*, 2S*)-2-(4-bromophenylsulfonyl amino)cyclopentyl]-5Z-heptenoic acid	0.20 (ethyl acetate : hexane = 1:1)	(KBr disk method) 3260, 2940, 1690, 1570, 1430, 1380, 1330, 1155, 1090, 1005, 905

table V (continued)

Example No.	Structure	Name	TLC (Rf)	IR (ν cm ⁻¹)
5 (i)		6-[(1S, 2S, 3S, 4R)-3-(4-bromophenyl sulfonaminoethyl)bicyclo[2.2.1]heptan-2-yl]-5Z-hexenoic acid	0.44 (ethyl acetate : hexane = 1:1)	(KBr disk method) 3260, 2920, 1680, 1310, 1140

55 Reference example 1

Synthesis of (1S,2S,3S,5R)-3-mesylamino-2-[2-(2-tetrahydropyranyl oxy)ethyl]-6,6-dimethylbicyclo[3.1.1]-heptane



5

10 Triethylamine (1.9 ml) was added to a solution of (1S,2S,3S,5R)-3-amino-2-[2-(2-tetrahydropyranyloxy)-ethyl]-6,6-dimethylbicyclo[3.1.1]heptane (3.25 g) in methylene chloride (30 ml). The reaction solution was cooled. To the above solution, mesyl chloride (1.0 ml) was dropped slowly. The reaction solution was allowed to stand for 1 hour. The reaction solution was extracted with methylene chloride. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate) to give the title compound (3.05 g) having the following physical data.

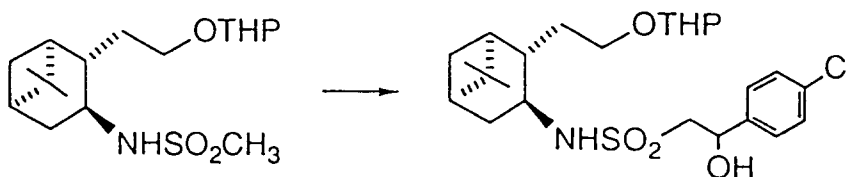
15 TLC: Rf 0.50 (hexane : ethyl acetate = 2:1);

MS: m/e 346, 277, 268, 262.

20 Reference example 2

Synthesis of (1S,2S,3S,5R)-3-[2-(4-chlorophenyl)-2-hydroxyethylsulfonyl]amino-2-[2-(2-tetrahydropyranyloxy)ethyl]-6,6-dimethylbicyclo[3.1.1]heptane

25



30

35 The compound prepared in reference example 1 (72.1 mg) was dissolved into the mixture of ether (1 ml) and tetramethylethylenediamine (0.22 ml) in dried container. A solution of n-butyl lithium in n-hexane (1.62 M, 0.45 ml) was added slowly to the reaction solution at room temperature. The reaction solution was stirred for 2 hours. A solution of 4-chlorobenzaldehyde (68.8 mg) in ether (1 ml) was added to the above solution. The mixture was stirred for 30 minutes. A saturated aqueous solution of ammonium chloride was added to the reaction solution. The mixture was allowed to stand for 5 minutes and extracted with a mixture solvent of n-hexane-ethyl acetate (1:1). The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate) to give the title compound (82 mg) having the following physical data.

40

TLC: Rf 0.60 (hexane : ethyl acetate = 3:2);

45

MS: m/e 400, 382, 332, 305.

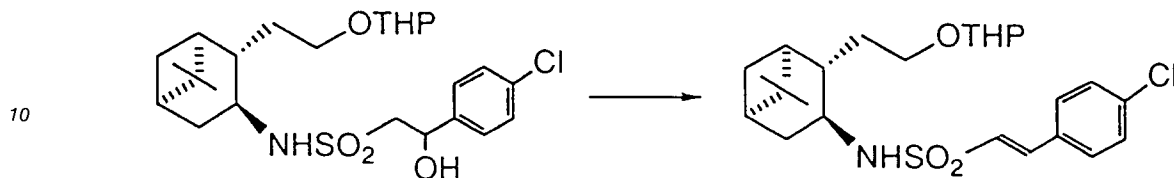
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Reference example 3

Synthesis of (1S,2S,3S,5R)-3-[2-(4-chlorophenyl)vinylsulfonylamino]-2-[2-(2-tetrahydropyranyloxy)ethyl]-6,6-dimethylbicyclo[3.1.1]heptane

5



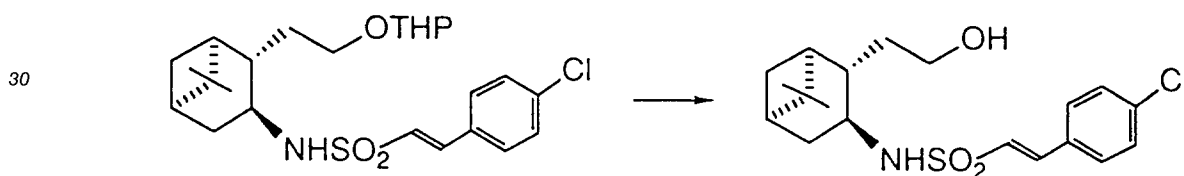
15

A mixture of the solution of the compound prepared in reference example 2 (258 mg) in methylene chloride (5 ml) and triethylamine (0.25 ml) was cooled. Mesyl chloride was dropped slowly to the above mixture. Ice-bath was removed. The mixture was stirred for 30 minutes. Water was added to the reaction solution. The above solution was extracted with methylene chloride. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate) to give the title compound (232 mg).

20

Reference example 4

25 Synthesis of (1S,2S,3S,5R)-3-[2-(4-chlorophenyl)vinylsulfonylamino]-2-(2-hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]heptane



35

p-Toluensulfonic acid (10 mg) was added to a solution of the compound prepared in reference example 3 (232 mg) in methanol (1.5 ml). The mixture was stirred for 1 hour at room temperature. Triethylamine was added to the reaction solution. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate) to give the title compound (187 mg) having the following physical data.

40

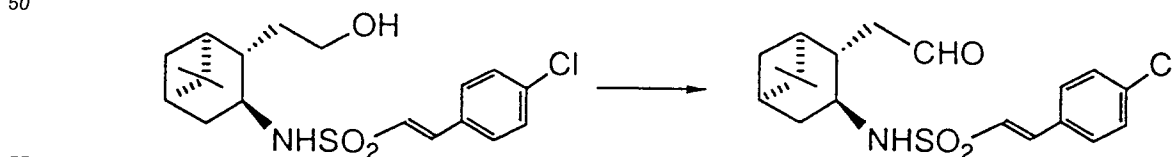
TLC: R_f 0.25 (hexane : ethyl acetate = 3:2);

MS: m/e 384, 368, 314, 298, 270.

45 Reference example 5

Synthesis of (1S,2S,3S,5R)-3-[2-(4-chlorophenyl)vinylsulfonylamino]-2-formylmethyl-6,6-dimethylbicyclo[3.1.1]heptane

50



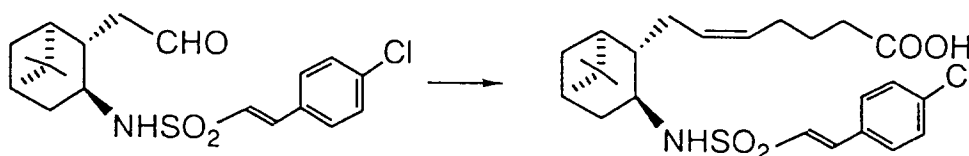
55

A solution of oxalyl chloride (0.07 ml) in methylene chloride (2 ml) was cooled at -70°C . To the above solution, a solution of DMSO (0.07 ml) in methylene chloride (2 ml) was dropped. The mixture was stirred for 10 minutes. A solution of the compound prepared in reference example 4 in methylene chloride (1 ml) was added to the reaction solution at same temperature. The mixture was stirred for 30 minutes.

5 Triethylamine (0.25 ml) was added to the reaction solution. Dry ice-bath was removed. The mixture was stirred for 30 minutes and extracted with ether. The organic layer was washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title compound.

Example 6

10 Synthesis of 7-[(1S,2S,3S,5R)-3-[2-(4-chlorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid



4-carboxybutyltriphenylphosphonium bromide (343 mg) and potassium t-butoxide (177 mg) was dissolved into THF (5 ml). The mixture was stirred for 10 minutes. A solution of the compound prepared in reference example 5 (113 mg) in THF (3 ml) was dropped to the reaction solution. The mixture was stirred for 1 hour. Water was added to the above mixture. The mixture solvent of ether-hexane (1:1) was added to the reaction solution. The above solution was separated. The water layer was acidified by adding 1N hydrochloride. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate) to give the title compound (105 mg) having the following physical data.

TLC: R_f 0.25 (hexane : ethyl acetate = 1:1);

MS: m/e 465, 447, 396, 378;

IR: ν 3271, 2922, 1708, 1309, 1144 cm^{-1} .

Example 6(1)~6(26)

By the same procedure as in reference example 1~5 and example 6, using corresponding starting materials and corresponding phosphonium salts, the title compound having the physical data shown in table VI, VII and VIII were given.

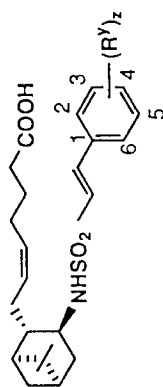


table VI

Example No.	(R') _x	Name	TLC (R _f)	IR (ν cm ⁻¹)
6 (1)	3 - F	7-[(1S, 2S, 3S, 5R)-3-[2-(3-fluorophenyl) vinylsulfonfylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.25 (ethyl acetate : hexane = 1:1)	3271, 2922, 1709, 1584, 1447, 1142
6 (2)	4 - F	7-[(1S, 2S, 3S, 5R)-3-[2-(4-fluorophenyl) vinylsulfonfylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.30 (ethyl acetate : hexane = 1:1)	3272, 2922, 1709, 1602, 1510, 1143
6 (3)	4 - Br	7-[(1S, 2S, 3S, 5R)-3-[2-(4-bromophenyl) vinylsulfonfylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.20 (ethyl acetate : hexane = 1:1)	3272, 2917, 1708

table VI (continued)

Example No.	(R ^Y) _x	Name	TLC (R _f)	IR (ν cm ⁻¹)
6 (4)	4 —CH ₃ O	7-[(1S, 2S, 3S, 5R)-3-[2-(4-methoxyphenyl) vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.30 (ethyl acetate : hexane = 1:1)	3272, 2921, 1708, 1423, 1259
6 (5)	4 —CH ₃	7-[(1S, 2S, 3S, 5R)-3-[2-(4-methylphenyl) vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.20 (ethyl acetate : hexane = 1:1)	3272, 2918, 1708, 1441, 1142
6 (6)	3 —CH ₃ O	7-[(1S, 2S, 3S, 5R)-3-[2-(3-methoxyphenyl) vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.21 (ethyl acetate : hexane = 1:1)	3272, 2921, 1708, 1580, 1434, 1142

table VI (continued)

Example No.	(R ^Y) _X	Name	TLC (Rf)	IR (ν cm ⁻¹)
6 (7)	3 —Br	7-[(1S, 2S, 3S, 5R)-3-[2-(3-bromophenyl) vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.25 (ethyl acetate : hexane = 1:1)	3272, 2921, 1708, 1439, 1143
6 (8)	2,6—diCH ₃	7-[(1S, 2S, 3S, 5R)-3-[2-(2,6-dimethylphenyl) vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.36 (ethyl acetate : hexane = 1:1)	3271, 2922, 1709, 1441, 1307, 1142
6 (9)	3 —CH ₃	7-[(1S, 2S, 3S, 5R)-3-[2-(3-methylphenyl) vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.30 (ethyl acetate : hexane = 1:2)	3272, 2922, 1708, 1440, 1331, 1141

table VI (continued)

Example No.	(R ^y) _x	Name	TLC (Rf)	IR (ν cm ⁻¹)
6 (10)	3 — Cl	7-[(1S, 2S, 3S, 5R)-3-[2-(3-chlorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.35 (ethyl acetate : hexane = 1:2)	3272, 2922, 1708, 1432, 1332, 1143
6 (11)	3 — CF ₃	7-[(1S, 2S, 3S, 5R)-3-[2-(3-trifluoromethylphenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.30 (ethyl acetate : hexane = 2:3)	3280, 2925, 1709, 1440, 1333, 1133
6 (12)	H	7-[(1S, 2S, 3S, 5R)-3-[2-phenylvinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.30 (ethyl acetate : hexane = 1:2)	3339, 2929, 1679, 1453, 1302, 1142

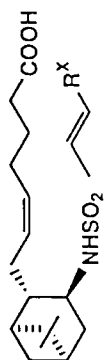


table VII


Example No.	R ^x	Name	TLC (Rf)	IR (ν cm ⁻¹)
6 (13)		7-[(1S, 2S, 3S, 5R)-3-(2-cyclohexylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.25 (ethyl acetate : hexane = 2:3)	3271, 2927, 1709, 1450, 1337, 1145
6 (14)	-C ₄ H ₉	7-[(1S, 2S, 3S, 5R)-3-(5E-hexenylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.30 (ethyl acetate : hexane = 1:2)	3339, 2929, 1679, 1453, 1302, 1142

table VII (continued)

Example No.	Structure	Name	TLC (Rf)	IR (ν cm ⁻¹)
6 (15)		7-[(1S, 2S, 3S, 5R)-3-(2-phenylvinylsulfonyl-N-methylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	0.24 (ethyl acetate : hexane = 1:1)	1708, 1616, 1577, 1450, 1336, 1142, 973
6 (16)		7-[(1S, 2S, 3S, 5R)-3-(2-phenylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-4Z-heptenoic acid	0.21 (ethyl acetate : hexane = 1:1)	3271, 1713, 1624, 1577, 1449, 1317, 1142, 1059, 972
6 (26)		7-[(1S, 2S, 3S, 5R)-3-(2-phenylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5E-heptenoic acid	0.13 (ethyl acetate : hexane = 1:1)	(KBr disk method) 3273, 2921, 1708, 1450, 1328, 1143

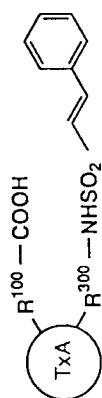


table VIII

Example No.		Name	TLC (Rf)	IR (ν cm ⁻¹)
6 (17)		7-[(1R, 2S, 3S, 4S)-3-(2-phenylvinyl sulfonamino)bicyclo[2.2.1]heptan-2-yl]-5Z-heptenoic acid	0.24 (ethyl acetate : hexane = 1:1)	3274, 1708, 1624, 1577, 1450, 1318, 1146, 973
6 (18)		6-[(1S, 2S, 3R, 4R)-3-(2-phenylvinyl sulfonaminomethyl)bicyclo[2.2.1]heptan-2-yl]-5Z-hexenoic acid	0.13 (ethyl acetate : hexane = 1:1)	3274, 1708, 1623, 1577, 1450, 1418, 1320, 1147, 972
6 (19)		7-[(1R*, 2S*)-2-(2-phenylvinylsulfonyl amino)cyclohexyl]-5Z-heptenoic acid	0.20 (ethyl acetate : hexane = 1:1)	3272, 1708, 1624, 1577, 1496, 1449, 1319, 1241, 1195, 1148, 1071, 971

table VIII (continued)

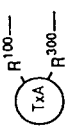

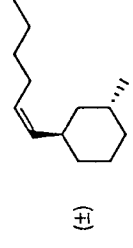
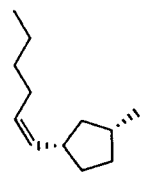
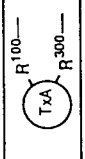
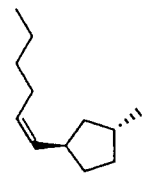
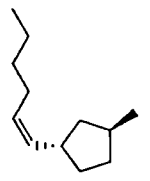
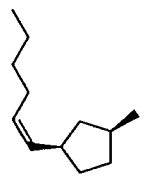
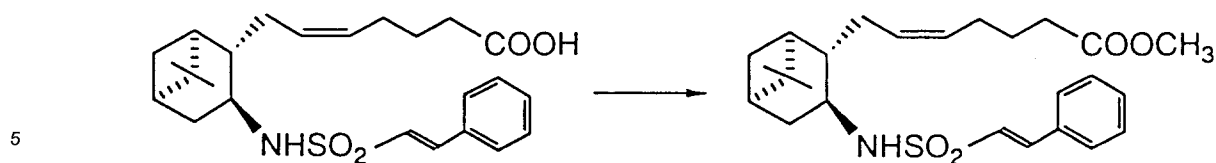
Example No.		Name	TLC (Rf)	IR (ν cm ⁻¹)
6 (20)		7-[(1S*, 2S*)-2-(2-phenylvinylsulfonyl amino)cyclohexyl]-5Z-heptenoic acid	0.17 (ethyl acetate : hexane = 1:1)	3292, 1708, 1623, 1577, 1451, 1326, 1148, 1005
6 (21)		6-[(1R*, 3R*)-3-(2-phenylvinylsulfonyl amino)cyclohexyl]-5Z-hexenoic acid	0.30 (ethyl acetate : hexane = 1:1)	3306, 2930, 1708, 1450, 1318, 1146
6 (22)		6-[(1S, 3R)-3-(2-phenylvinylsulfonylamino) cyclopentyl]-5Z-hexenoic acid	0.28 (ethyl acetate : hexane = 1:1)	3307, 2930, 1708, 1451, 1303

table VIII (continued)

Example No.		Name	TLC (Rf)	IR (ν cm ⁻¹)
6 (23)		6-[(1R, 3R)-3-(2-phenylvinylsulfonyl amino)cyclopentyl]-5Z-hexenoic acid	0.25 (ethyl acetate : hexane = 1:1)	3307, 2990, 1707, 1451, 1317
6 (24)		6-[(1S, 3S)-3-(2-phenylvinylsulfonyl amino)cyclopentyl]-5Z-hexenoic acid	0.25 (ethyl acetate : hexane = 1:1)	3272, 2952, 1708, 1449, 1318, 1145
6 (25)		6-[(1R, 3S)-3-(2-phenylvinylsulfonyl amino)cyclopentyl]-5Z-hexenoic acid	0.28 (ethyl acetate : hexane = 1:1)	3307, 2930, 1708, 1451, 1303

Example 7

Synthesis of 7-[(1S,2S,3S,5R)-3-(2-phenylvinylsulfonylamino)-6,6-dimethyl bicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid methyl ester

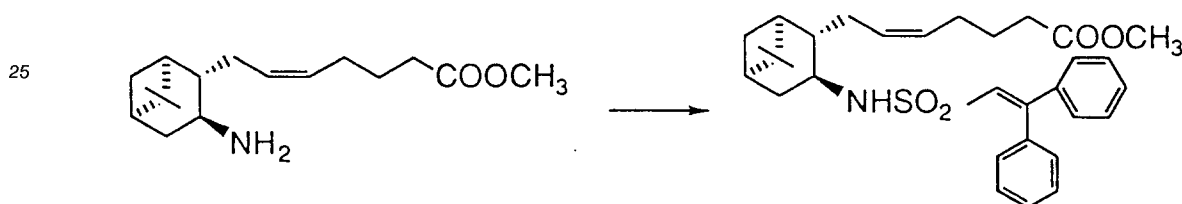


10 To a solution of the compound prepared in example 6(12) (97 mg) in methanol (5 ml), a solution of diazomethane in ether was added till the mixture showed a yellow color at 0 °C. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane) to give the title compound (90 mg) having the following physical data.

15 TLC: R_f 0.38 (ethyl acetate : hexane = 1:2);
IR: ν 3274, 1738, 1624, 1577, 1438, 1332, 1146, 1061, 973 cm⁻¹.

Example 8

20 Synthesis of 7-[(1S,2S,3S,5R)-3-(2,2-diphenylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid methyl ester

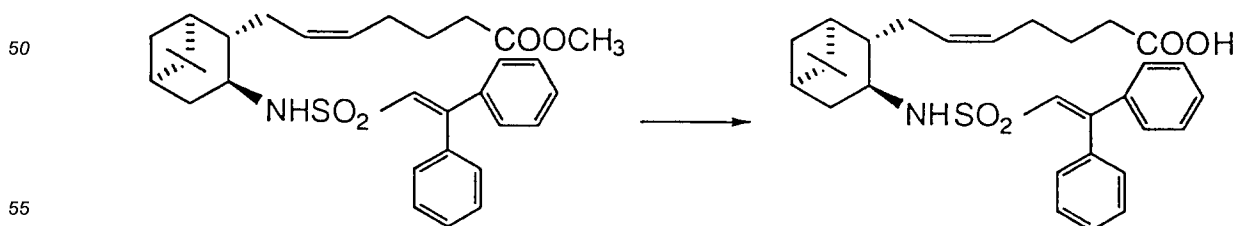


35 7-[(1S,2S,3S,5R)-3-amino-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid methyl ester (The compound was described as reference example 14 in specification of the United States Patent No. 4792550; 145 mg) and triethylamine (0.21 ml) were dissolved into methylene chloride (5 ml) and the mixture was cooled with ice-bath. 2,2-Diphenylvinylsulfonyl chloride (188 mg) was added to the above solution. The mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into 1N hydrochloric acid (5 ml) and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine, successively, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3% ethyl acetate / hexane) to give the title compound (203 mg) having the following physical data.

TLC: R_f 0.29 (hexane : ethyl acetate = 3 : 1)

Example 9

45 Synthesis of 7-[(1S,2S,3S,5R)-3-(2,2-diphenylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid



To a mixed solution of dimethoxyethane (3 ml) and methanol (1.5 ml) of the compound prepared in example 8 (191 mg), 2N sodium hydride solution (1 ml) was added. The mixture was stirred for 4 hours at room temperature. After solvent was distilled off the reaction mixture, ice and 1N hydrochloric acid (2 ml) were added to the residue. The above solution was extracted with ethyl acetate. The organic layer was washed with water and brine, successively, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1 → 1 : 2 (0.1% acetic acid)) to give the title compound (101 mg) having the following physical data.

TLC : R_f 0.21 (hexane : ethyl acetate = 1 : 1);

NMR: δ 7.48-7.22 (10H, m), 6.87 (1H, s), 5.49-5.26 (2H, m), 4.58 (1H, d), 3.73 (1H, m), 2.60-1.84 (10H, m), 1.80-1.47 (4H, m), 1.18 (3H, s), 0.98 (3H, s), 0.70 (1H, d).

Formulation example 1: Preparation of tablets

The following compounds were admixed in conventional method and punched out to obtain 100 tablets each containing 100 mg of active ingredient.

• 7-[(1S,2S,3S,5R)-3-tosylamino-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid	10 g
• Cellulose calcium glycolate (disintegrating agent)	200 mg
• Magnesium stearate (lubricating agent)	100 mg
• Micro crystalline cellulose	9.7 g

Formulation example 2: Preparation of tablets

The following compounds were admixed in conventional method and punched out to obtain 100 tablets each containing 100 mg of active ingredient.

• 7-[(1S,2S,3S,5R)-3-[2-(4-chlorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid	10g
• Cellulose calcium glycolate (disintegrating agent)	200 mg
• Magnesium stearate (lubricating agent)	100 mg
• Micro crystalline cellulose	9.7 g

Formulation example 3: Preparation of injections

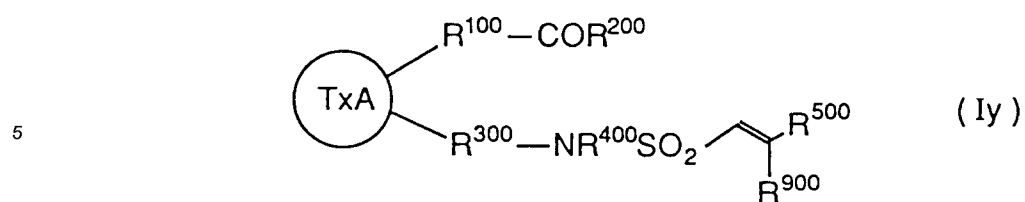
7-[(1S,2S,3S,5R)-3-tosylamino-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid (5g) and mannitol (50g) were dissolved by adding distilled water. Then, distilled water was added thereto to make the total volume 500 ml. The solution was filtrated by a bacteria-retaining filter. The solution was placed in 5 ml portion in 10 ml vial in usual way and freeze-dried to obtain 100 vials each containing 50 mg of active ingredient.

Formulation example 4: Preparation of injections

7-[(1S,2S,3S,5R)-3-[2-(4-chlorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid (5g) and mannitol (50g) were dissolved by adding distilled water. Then, distilled water was added thereto to make the total volume 500 ml. The solution was filtrated by a bacteria-retaining filter. The solution was placed in 5 ml portion in 10 ml vial in usual way and freeze-dried to obtain 100 vials each containing 50 mg of active ingredient.

Claims

1. Carbocyclic sulfonamides of the formula:

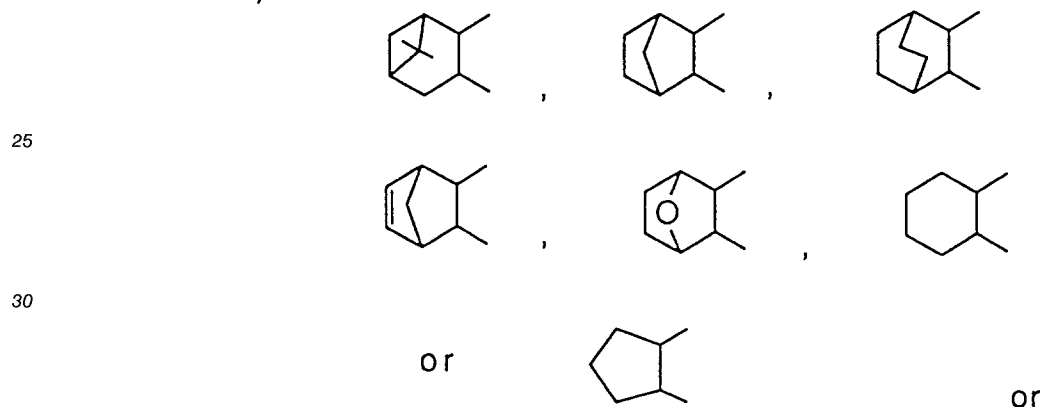


10 wherein

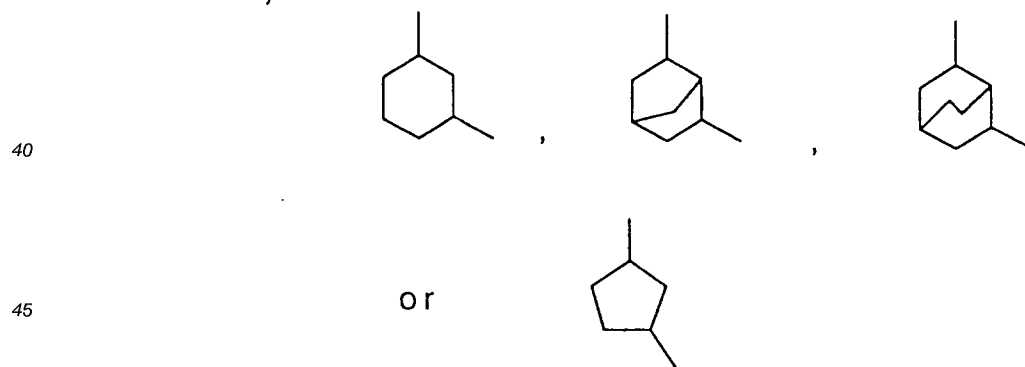


is

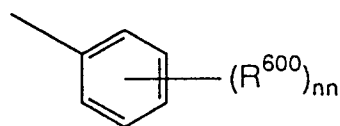
20 i)



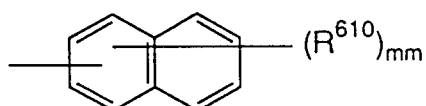
35 ii)



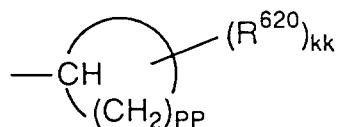
50 R^{100} is C4-7 alkylene or C4-7 alkenylene;
 R^{200} is hydroxy, C1-20 alkoxy of $\text{NR}^{230}\text{R}^{240}$
in which R^{230} and R^{240} each, independently, is hydrogen, C1-4 alkyl or $\text{NR}^{230}\text{R}^{240}$ is amino acid
residue;
 R^{300} is a single bond or C1-4 alkylene;
55 R^{400} is hydrogen or C1-4 alkyl;
 R^{500} and R^{900} each, independently, is
i)



in which R^{600} is hydrogen, C1-4 alkyl, C1-4 alkoxy, hydroxy, halogen, trifluoromethyl, nitro;
nn is 1, 2 or 3;
ii)

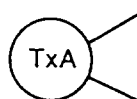


in which R^{610} is hydrogen, C1-4 alkyl, C1-4 alkoxy, hydroxy, halogen, trifluoromethyl, nitro;
mm is 1, 2 or 3;
iii)

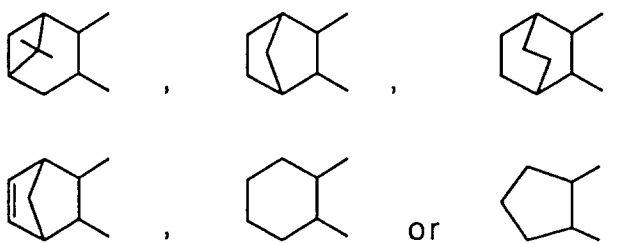


in which R^{620} is hydrogen, C1-4 alkyl, C1-4 alkoxy, hydroxy, halogen, trifluoromethyl, nitro;
kk is 1, 2 or 3;
pp is 3, 4, 5, or 6;
iv) C1-7 alkyl or
v) hydrogen ;
cyclodextrin clathrates thereof or non-toxic salts thereof.

2. A compound according to claim 1, wherein

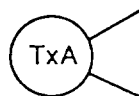


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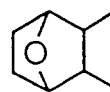


3. A compound according to claim 1, wherein

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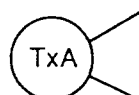
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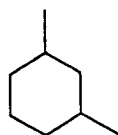
4. A compound according to claim 1, wherein

15

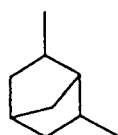


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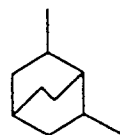
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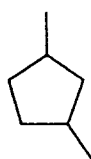


,



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or

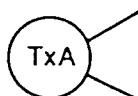


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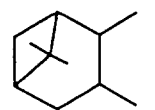
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5. A compound according to claim 2, wherein

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is



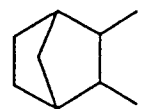
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6. A compound according to claim 2, wherein

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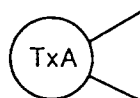


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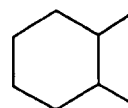


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7. A compound according to claim 2, wherein



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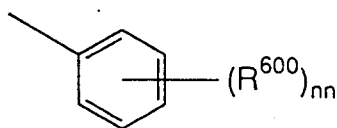


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8. A compound according to claim 2, wherein R^{100} is pentenylene or hexenylene, R^{300} is a single bond or methylene.

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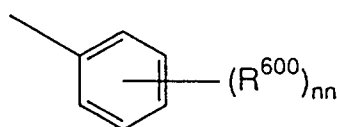
9. A compound according to claim 2, wherein R^{500} is the formula:



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wherein all the symbols are the same meaning as defined in claim 1, and R^{900} is hydrogen or the formula:



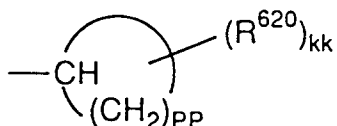
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30

wherein all the symbols are the same meaning as defined in claim 1.

10. A compound according to claim 2, wherein R^{500} is

35



40

wherein all the symbols are the same meaning as hereinbefore defined, or C1-7 alkyl and R^{900} is hydrogen.

45 11. A compound according to claim 1, which is

7-[3-[2-(4-chlorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid methyl ester,

7-[3-(2-phenylvinylsulfonyl-N-methylamino)-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

50

7-[3-(2-phenylvinylsulfonylamino)-6,6-dimethyl bicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid,

7-[3-[2-(3-fluorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

7-[3-[2-(4-fluorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

55

7-[3-[2-(4-bromophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

7-[3-[2-(4-chlorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

7-[3-[2-(4-methoxyphenyl)vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid,

7-[3-[2-(4-methylphenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

5 7-[3-[2-(3-methoxyphenyl)vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1]heptan-2-yl]-5Z-heptenoic acid,

7-[3-[2-(3-bromophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

10 7-[3-[2-(2,6-dimethylphenyl)vinylsulfonylamino]-6,6-dimethylbicyclo [3.1.1] heptan-2-yl]-5Z-heptenoic acid,

7-[3-[2-(3-methylphenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

7-[3-[2-(3-chlorophenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

15 7-[3-[2-(3-trifluoromethylphenyl)vinylsulfonylamino]-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid,

7-[3-(2-phenylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5Z-heptenoic acid,

7-[3-(2-phenylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]-5E-heptenoic acid,

7-[3-(2,2-diphenylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

20 7-[3-(2-cyclohexylvinylsulfonylamino)-6,6-dimethylbicyclo[3.1.1] heptan-2-yl]-5Z-heptenoic acid,

7-[3-(5Z-hexenylsulfonylamino)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl] -5Z-heptenoic acid,

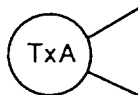
7-[3-(2-phenylvinylsulfonylamino)bicyclo[2.2.1]heptan-2-yl]-5Z-heptenoic acid,

7-[3-(2-phenylvinylsulfonylaminomethyl)bicyclo[2.2.1]heptan-2-yl]-5Z-hexenoic acid or

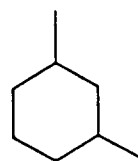
7-[2-(2-phenylvinylsulfonylamino)cyclohexyl]-5Z-heptenoic acid.

25 **12.** A compound according to claim 4, wherein

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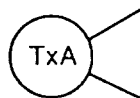
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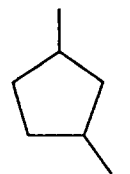
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13. A compound according to claim 4, wherein

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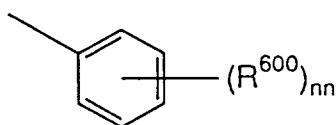
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14. A compound according to claim 4, wherein R^{100} is pentenylene, R^{300} is a single bond, R^{500} is

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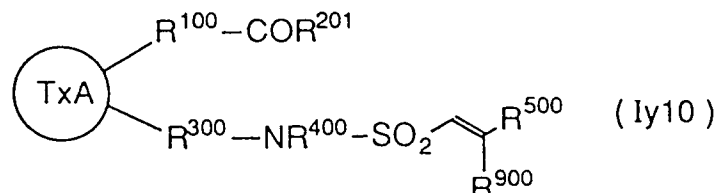
wherein all the symbols are the same meaning as defined in claim 1, and R^{900} is hydrogen.

15. A compound according to claim 1, which is

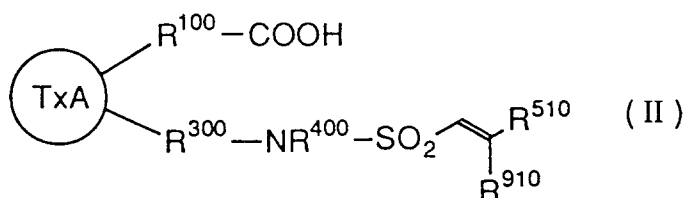
6-[3-(2-phenylvinylsulfonylamino)cyclohexyl]-5Z-hexenoic acid or

6-[3-(2-phenylvinylsulfonylamino)cyclopentyl]-5Z-hexenoic acid.

16. A process for the preparation of the compound of the formula:

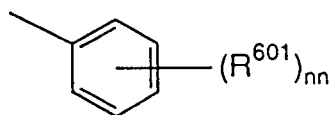


wherein R^{201} is C1-20 alkoxy or $NR^{230}R^{240}$, in which R^{230} and R^{240} is the same meaning as defined in claim 1, which is characterized by subjecting the compound of the formula:



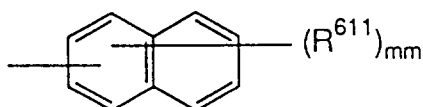
wherein R^{510} and R^{910} each, independently, is

i)



in which R^{601} is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro or 2-tetrahydropyranyloxy, nn is 1, 2 or 3, or

ii)



in which R^{611} is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro or 2-tetrahydropyranyloxy, mm is 1, 2 or 3, or

iii)



v) hydrogen,

15

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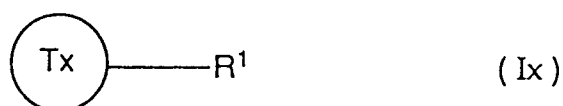


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wherein R^1 is

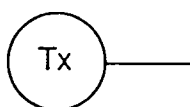
i) COOR^{11} or

ii) $\text{CONR}^{13}\text{R}^{14}$

in which R^{11} is hydrogen, C1-20 alkyl;

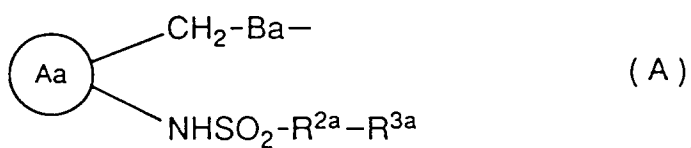
R^{13} and R^{14} each, independently, is hydrogen, C1-4 alkyl or

$\text{NR}^{13}\text{R}^{14}$ is amino acid residue;

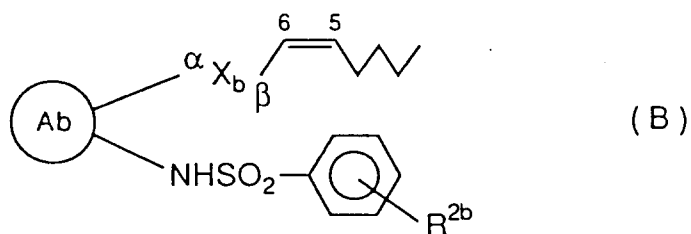


is

i)

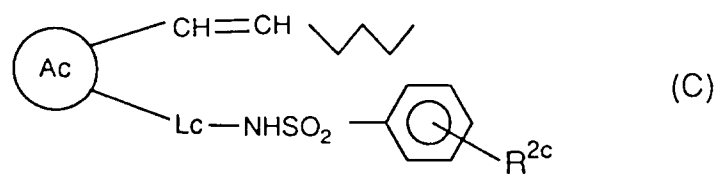


ii)

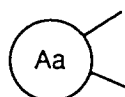


or

iii)



in which



is

5

i)



(Aa - 1) ,

10

ii)



(Aa - 2) ,

15

iii)



(Aa - 3) ,

20

iv)



(Aa - 4) ,

25

v)



(Aa - 5) ,

30

vi)



(Aa - 6)

or

vii)



(Aa - 7) ;

35

Ba is

i) $-\text{CH}_2-\text{CH}_2(\text{CH}_2)_m-$ (Ba-1) or

40

ii) $\text{cis-CH}=\text{CH}-(\text{CH}_2)_m-$ (Ba-2)

in which m is 1-6;

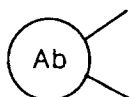
R^{2a} is a single bond or C1-4 alkylene;

R^{3a} is benzene, naphthalene or C4-7 cycloalkyl unsubstituted or substituted by one to three of C1-4 alkyl, C1-4 alkoxy, hydroxy, cyano, halogen, trifluoromethyl or nitro or

45

R^{2a} and R^{3a} taken together, is C1-12 alkyl;

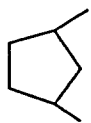
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is

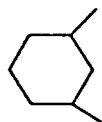
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i)



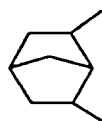
(Ab - 1) ,

ii)



(Ab - 2) ,

iii)



(Ab - 3)

or

iv)



(Ab - 4)

;

Xb is

i) a single bond,

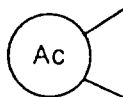
ii) C1-4 alkylene or

iii) C2-4 alkenylene,

with the proviso that, $\alpha\text{CH}=\text{CHCH}_2^\beta$ and $\alpha\text{CH}_2\text{CH}=\text{CHCH}_2^\beta$ are excluded;

R^{2b} is hydrogen, C1-4 alkyl, C1-4 alkoxy, hydroxy, cyano, halogen, trifluoromethyl or nitro;

the configuration of a double bond between C5-C6 in the formula (B) is cis;



is

5

i)



(Ac - 1) ,

10

ii)



(Ac - 2) ,

15

iii)



(Ac - 3) ,

20

iv)



(Ac - 4) ,

25

v)



(Ac - 5) ,

30

vi)



(Ac - 6) ,

35

vii)



(Ac - 7)

or

40

viii)



(Ac - 8) ;

Lc is C1-4 alkylene;

45

R^{2C} is hydrogen, C1-4 alkyl, C1-4 alkoxy, hydroxy, cyano, halogen, trifluoromethyl or nitro;

the configuration of a double bond between C5-C6 in the formula (c) is cis or trans ;

cyclodextrin clathrates thereof or non-toxic acid salts thereof, when R¹¹ is hydrogen or NR¹³R¹⁴ is

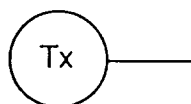
amino acid residue, for use in the manufacture of pharmaceutical composition for prevention and/or

50

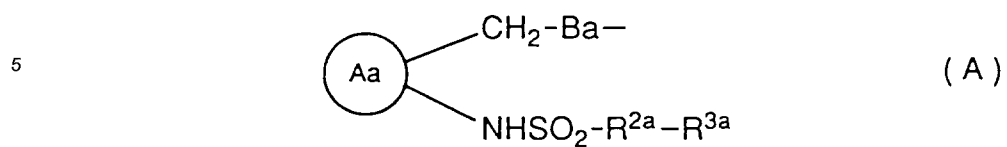
treatment of abortion, pain, diarrhea, insomnia, constipation, ulcer, gastritis or hypertension, or for induction of labour in pregnant female mammals.

21. A compound according to claim 20, wherein

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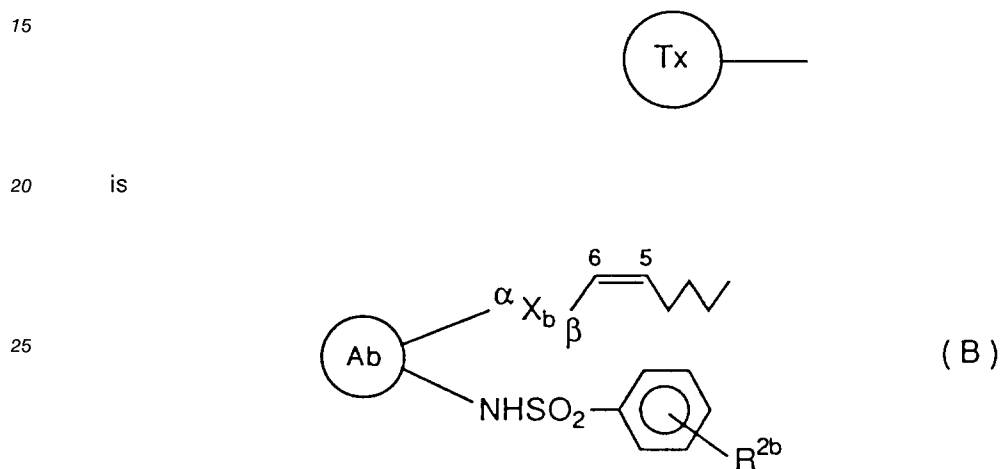


is



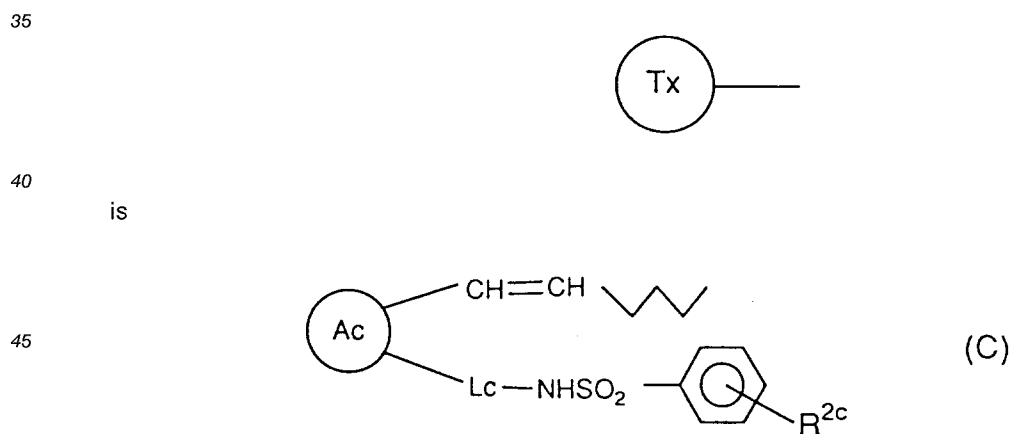
10 wherein all the symbols are the same meaning as defined in claim 20.

22. A compound according to claim 20, wherein



30 wherein all the symbols are the same meaning as defined in claim 20.

23. A compound according to claim 20, wherein



50 wherein all the symbols are the same meaning as defined in claim 20.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 10 1085

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
D,A	US-A-5 168 101 (Y. ARAI, et al.) * column 2 - column 5 * ---	1-19	C07C311/13 C07C311/20 C07C311/07
D,A	US-A-4 861 913 (F. WATANABE, et al.) * column 1 - column 2 * -----	1-19	C07C311/12 C07C311/27 C07C311/29 C07C311/10 C07C311/11 A61K31/18
			TECHNICAL FIELDS SEARCHED (Int.Cl.5)
			C07C
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 10 May 1994	Examiner English, R
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			